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【Claim to Priority Based on an Earlier Application】

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【Claim to Priority Based on an Earlier Application】

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【Filing Date】 July 24, 2003

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【List of Submitted Items】

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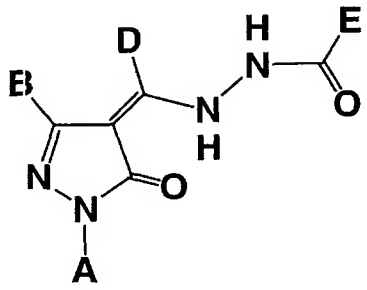
【Name of item】	Abstract	1

【Type of Document】 SCOPE OF THE CLAIM(S)

【Claim 1】

A pyrazolone compound represented by the formula (1)

【Ka 1】



(1)

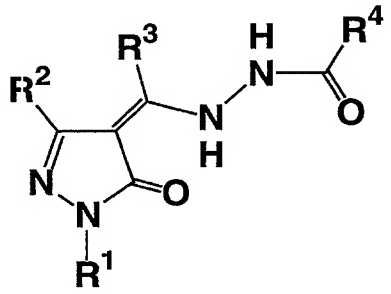
[wherein A is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), B is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, D is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and E is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more halogen atoms, NG^1G^2 (wherein G^1 and G^2 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl

groups or C_{1-6} alkylcarbonyl groups), one or more carboxyl groups, one or more sulfonic acid groups, one or more phosphonic acid groups, one or more carbamido groups, one or more sulfamido groups, one or more hydroxycarbamido groups, one or more hydroxysulfamido groups, one or more tetrazole groups, one or more C_{1-6} alkoxycarbonyl groups or $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NG^3 (G^3 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 2】

A pyrazolone compound represented by the formula (2)

【Ka 2】



(2)

[wherein R^1 is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups

(the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^2 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^3 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and R^4 is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more hydroxyl groups, one or more nitro groups or NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 3】

The pyrazolone compound according to Claim 2, wherein R^4 is a C_{2-14} aryl group substituted with one or more hydroxyl groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 4】

The pyrazolone compound according to Claim 2, wherein R^4 is a C_{2-14} aryl group substituted with NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 5】

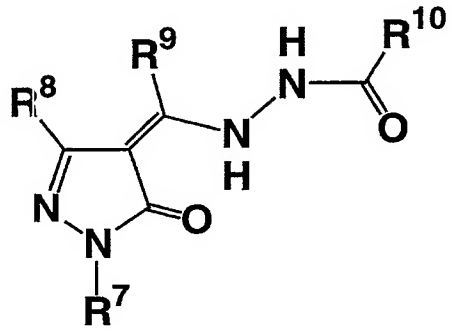
The pyrazolone compound according to Claim 2, wherein

R^4 is a C_{2-14} aryl group substituted with one or more nitro groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 6】

A pyrazolone compound represented by the formula (3)

【Ka 3】



(3)

[wherein R^7 is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^8 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^9 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and R^{10} is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more carboxyl groups, one or more sulfonic

acid groups, one or more phosphonic acid groups, one or more carbamido groups, one or more sulfamido groups, one or more hydroxycarbamido groups, one or more hydroxysulfamido groups, one or more tetrazole groups, one or more C_{1-6} alkoxycarbonyl groups or $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 7】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with one or more carboxyl groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound, or a solvate thereof.

【Claim 8】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3), a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 9】

The pyrazolone compound according to Claim 6, wherein

R^{10} is a C_{2-14} aryl group substituted with one or more sulfonic acid groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 10】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with one or more phosphonic acid groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 11】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with one or more tetrazole groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 12】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with one or more carbamido groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

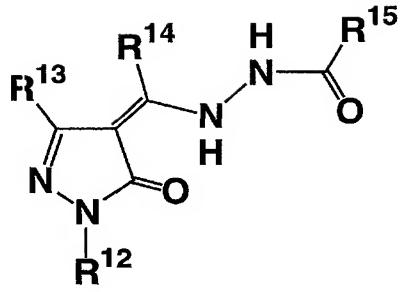
【Claim 13】

The pyrazolone compound according to Claim 6, wherein R^{10} is a C_{2-14} aryl group substituted with one or more sulfamido groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 14】

A pyrazolone compound represented by the formula (4)

【Ka 4】



(4)

[wherein R^{12} is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^{13} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^{14} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and R^{15} is a C_{2-14} aryl group (the C_{2-14} aryl group is substituted with a substituent selected from a hydroxyl group, an amino group, a nitro group and a halogen atom and with a substituent selected from a carboxyl group, a sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido group, a hydroxycarbamido group, a hydroxysulfamido group, a tetrazole group, a C_{1-6}

alkoxycarbonyl group and $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 15】

The pyrazolone compound according to Claim 14, wherein R^{15} is a C_{2-14} aryl group substituted with a hydroxyl group and a carboxyl group, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 16】

The pyrazolone compound according to Claim 14, wherein R^{15} is a C_{2-14} aryl group substituted with an amino group and a carboxyl group, a tautomer, a prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 17】

The pyrazolone compound according to Claim 14, wherein R^{15} is a C_{2-14} aryl group substituted with a substituent selected from a nitro group and a halogen atom and with a carboxyl group, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 18】

The thrombopoietin receptor activator according to Claim 1.

【Claim 19】

The thrombopoietin receptor activator according to Claim 2.

【Claim 20】

The thrombopoietin receptor activator according to Claim 3.

【Claim 21】

The thrombopoietin receptor activator according to Claim 4.

【Claim 22】

The thrombopoietin receptor activator according to Claim 5.

【Claim 23】

The thrombopoietin receptor activator according to Claim 6.

【Claim 24】

The thrombopoietin receptor activator according to Claim 7.

【Claim 25】

The thrombopoietin receptor activator according to Claim 8.

【Claim 26】

The thrombopoietin receptor activator according to Claim 9.

【Claim 27】

The thrombopoietin receptor activator according to Claim 10.

【Claim 28】

The thrombopoietin receptor activator according to Claim 11.

【Claim 29】

The thrombopoietin receptor activator according to Claim 12.

【Claim 30】

The thrombopoietin receptor activator according to Claim 13.

【Claim 31】

The thrombopoietin receptor activator according to Claim 14.

【Claim 32】

The thrombopoietin receptor activator according to Claim 15.

【Claim 33】

The thrombopoietin receptor activator according to Claim 16.

【Claim 34】

The thrombopoietin receptor activator according to Claim 17.

【Claim 35】

A preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin

receptor is effective, which contains the thrombopoietin receptor activator according to Claim 18, Claim 19, Claim 20, Claim 21, Claim 22, Claim 23, Claim 24, Claim 25, Claim 26, Claim 27, Claim 28, Claim 29, Claim 30, Claim 31, Claim 32, Claim 33 or Claim 34, a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【Claim 36】

A platelet increasing agent containing the thrombopoietin receptor activator according to Claim 18, Claim 19, Claim 20, Claim 21, Claim 22, Claim 23, Claim 24, Claim 25, Claim 26, Claim 27, Claim 28, Claim 29, Claim 30, Claim 31, Claim 32, Claim 33 or Claim 34, a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【Type of Document】 DESCRIPTION

【Title of the invention】

PYRAZOLONE COMPOUNDS AND THROMBOPOIETIN RECEPTOR ACTIVATOR

【Technical field】

The present invention relates to preventive, therapeutic and improving agents having affinity for and agonistic action on the thrombopoietin receptor for diseases against which activation of the thrombopoietin receptor is effective. Specifically, it relates to pharmaceutical compositions comprising compounds which increase platelets through stimulation of differentiation and proliferation of hematopoietic stem cells, megakaryocytic progenitor cells and megakaryocytes or compounds for therapeutic angiogenesis or with anti-arteriosclerosis action that stimulate differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells.

【Background art】

Thrombopoietin is a cytokine consisting of 332 amino acids that increases platelet production by stimulating differentiation and proliferation of hematopoietic stem cells, megakaryocytic progenitor cells and megakaryocytes mediated by its receptor and therefore is promising as a drug for hematological disorders. Recent reports that it stimulates differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells have

raised expectations of therapeutic angiogenesis, anti-arteriosclerosis and prevention of cardiovascular events (for example, non-patent document 1, non-patent document 2 and non-patent document 3).

Biologically active substances which have been known so far to regulate platelet production through the thrombopoietin receptor include, in addition to thrombopoietin itself, low molecular weight peptides having affinity for the thrombopoietin receptor (for example, patent document 1, patent document 2, patent document 3 and patent document 4).

As a result of search for nonpeptidic low molecular weight compounds that increase platelet production mediated by the thrombopoietin receptor, low molecular weight compounds having affinity for the thrombopoietin receptor have been reported (for example, patent document 5 to patent document 22).

1) Applications filed by Hokuriku Seiyaku Co., Ltd. relating to 1,4-benzodiazepine derivatives (patent documents 5 and 6)

2) International Laid-open Patent Applications filed by Shionogi & Co., Ltd. (patent documents 7-10)

3) International Laid-open Patent Applications filed by SmithKline Beecham Corp (patent documents 11-19)

4) Japanese Laid-open Patent Application filed by Torii Pharmaceutical Co., Ltd. (patent document 20)

5) International Laid-open Patent Application filed by

Roche Diagnostics GMBH (patent document 21)

6) International Laid-open Patent Application filed by Yamanouchi Pharmaceutical Co., Ltd. (patent document 22)

Some reports have been made about pyrazolone compounds (such as non-patent documents 4-13).

【Patent Document 1】 JP-A-10-72492

【Patent Document 2】 WO96/40750

【Patent Document 3】 WO96/40189

【Patent Document 4】 WO98/25965

【Patent Document 5】 JP-A-11-1477

【Patent Document 6】 JP-A-11-152276

【Patent Document 7】 WO01/07423

【Patent Document 8】 WO01/53267

【Patent Document 9】 WO02/059099

【Patent Document 10】 WO02/059100

【Patent Document 11】 WO00/35446

【Patent Document 12】 WO00/66112

【Patent Document 13】 WO01/34585

【Patent Document 14】 WO01/17349

【Patent Document 15】 WO01/39773

【Patent Document 16】 WO01/21180

【Patent Document 17】 WO01/89457

【Patent Document 18】 WO02/49413

【Patent Document 19】 WO02/085343

【Patent Document 20】 JP-A-2001-97948

【Patent Document 21】 WO99/11262

【Patent Document 22】 WO02/062775

【Non-patent Document 1】 Microvasc. Res., 1999: 58, p.108-113

【Non-patent Document 2】 Circ. Res., 1999: 84, p.785-796

【Non-patent Document 3】 Blood 2001:98, p.71a

【Non-patent Document 4】 Huaxue Xuebao (2001), 59(9) p.1495-1501

【Non-patent Document 5】 Synthesis and Reactivity in Inorganic andMetal Organic Chemistry (2000), 30(7) p.1265-1271

【Non-patent Document 6】 Synthesis and Reactivity in Inorganic andMetal Organic Chemistry (2002), 32(4) p.739-751

【Non-patent Document 7】 Synthesis and Reactivity in Inorganic andMetal Organic Chemistry (2002), 32(5) p.903-912

【Non-patent Document 8】 Jiegou Huaxue (2002), 21(5), p.553-556

【Non-patent Document 9】 Polyhedroon (1997), 16(11) p.1825-1829

【Non-patent Document 10】 Arzneim-Forsch (1969), 19(10) p.1721-1723

【Non-patent Document 11】 Structural Chemistry (1999), 10(2), 105-119

【Non-patent Document 12】 Chemical Sciences (1996), 51(9), 1240-1244

【Non-patent Document 13】 Chemical Sciences (1997),

52(2), 237-242

【Disclosure of Invention】

【Problems to be solved by the invention】

Thrombopoietin and low molecular weight peptides having affinity for the thrombopoietin receptor are likely to be easily degraded in the gastrointestinal tract and are usually difficult to orally administer. As to thrombopoietin itself, the appearance of anti-thrombopoietin antibodies have been reported.

Besides, though it is probably possible to orally administer nonpeptidic low molecular weight compounds, no practical drugs have been put on the market.

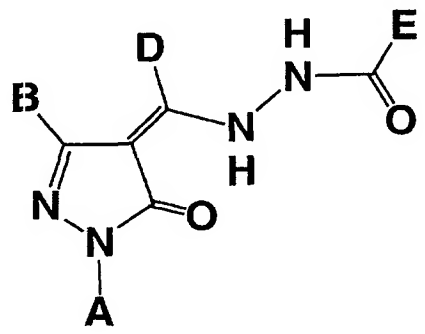
Therefore, orally administrable low molecular weight compounds having excellent affinity for and agonistic action on the thrombopoietin receptor as preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective have been demanded. Specifically, low molecular weight compounds which can serve as platelet increasing agents or increasing agents for other blood cells by stimulating differentiation and proliferation of hematopoietic stem cells, megakaryocytic progenitor cells and megakaryocytes or low molecular weight compounds which can be used for therapeutic angiogenesis or as preventive and therapeutic agents for arteriosclerosis by stimulating endothelial cells and endothelial progenitor cells have been demanded.

【Means for solving problem】

The present inventors conducted extensive research to find low molecular weight compounds having affinity for and agonistic action on the thrombopoietin receptor, and as a result, found that the compounds of the present invention have high affinity and agonistic action which enable them to show potent platelet increasing action by stimulating differentiation and proliferation of megakaryocytic progenitor cells and megakaryocytes. The present invention was accomplished on the basis of this discovery.

Namely, the present invention relates to a pyrazolone compound represented by the formula (1)

【Ka 5】



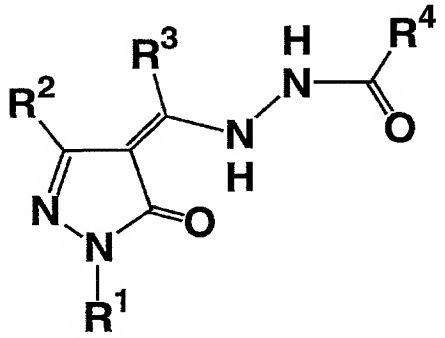
(1)

[wherein A is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be

substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), B is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, D is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and E is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more halogen atoms, NG^1G^2 (wherein G^1 and G^2 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), one or more carboxyl groups, one or more sulfonic acid groups, one or more phosphonic acid groups, one or more carbamido groups, one or more sulfamido groups, one or more hydroxycarbamido groups, one or more hydroxysulfamido groups, one or more tetrazole groups, one or more C_{1-6} alkoxycarbonyl groups or $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NG^3 (G^3 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof, a thrombopoietin receptor activator, a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective which contains the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the

thrombopoietin receptor activator or a solvate thereof as an active ingredient, and a platelet increasing agent containing the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient. It also relates to a pyrazolone compound represented by the formula (2)

【Ka 6】

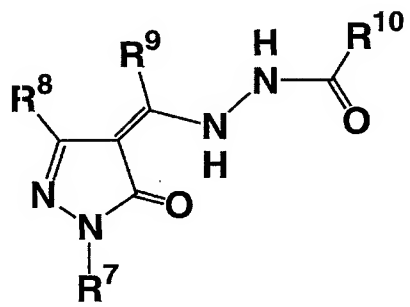


(2)

[wherein R^1 is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^2 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^3 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more

fluorine atoms or a C_{2-14} aryl group, and R^4 is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more hydroxyl groups, one or more nitro groups or NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof, a thrombopoietin receptor activator, a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective which contains the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient, and a platelet increasing agent containing the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient. It further relates to a pyrazolone compound represented by the formula (3)

【Ka 7】

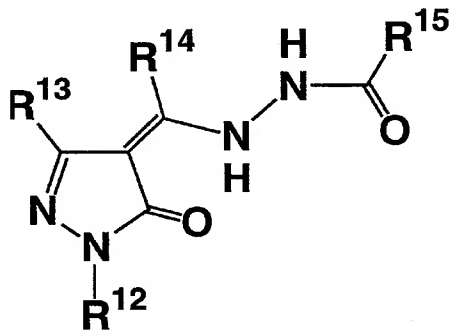


(3)

[wherein R^7 is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^8 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^9 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and R^{10} is a C_{2-14} aryl group (the C_{2-14} aryl group is optionally substituted with one or more carboxyl groups, one or more sulfonic acid groups, one or more phosphonic acid groups, one or more carbamido groups, one or more sulfamido groups, one or more hydroxycarbamido groups, one or more hydroxysulfamido groups, one or more tetrazole groups, one or more C_{1-6} alkoxycarbonyl groups or $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof, a thrombopoietin receptor activator, a preventive, therapeutic or improving agent

for diseases against which activation of the thrombopoietin receptor is effective which contains the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient, and a platelet increasing agent containing the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient. It still further relates to a pyrazolone compound represented by the formula (4)

【Ka 8】



(4)

[wherein R^{12} is a C_{2-14} aryl group (the C_{2-14} aryl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl

group)), R^{13} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, R^{14} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and R^{15} is a C_{2-14} aryl group (the C_{2-14} aryl group is substituted with a substituent selected from a hydroxyl group, an amino group, a nitro group and a halogen atom and with a substituent selected from a carboxyl group, a sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido group, a hydroxycarbamido group, a hydroxysulfamido group, a tetrazole group, a C_{1-6} alkoxycarbonyl group and $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3))], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof, a thrombopoietin receptor activator, a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective which contains the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient, and a platelet increasing agent containing the thrombopoietin receptor activator, a tautomer, prodrug or

pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient.

Though WO99/11262 (patent document 21), WO01/34585 (patent document 13), WO02/49413 (patent document 18) disclose pyrazolone compounds having platelet increasing action, there is no specific disclosure of the pyrazolone compounds of the present invention. The compounds of the present invention showed high activity that could not be expected from the disclosure in WO99/11262 (patent document 21), WO01/34585 (patent document 13) or WO02/49413 (patent document 18).

【Best mode(s) for carrying out the invention】

Now, the present invention will be described in detail.

In the present invention, "n" denotes normal, "i" denotes iso, "s" denotes secondary, "t" denotes tertiary, "c" denotes cyclo, "o" denotes ortho, "m" denotes meta, "p" denotes para, "Ph" denotes phenyl, "Py" denotes pyridyl, "Naphthyl" denotes naphthyl, "Me" denotes methyl, "Et" denotes ethyl, "Pr" denotes propyl, and "Bu" denotes butyl.

First, the terms in the respective substituents A, B, D, E, G^1, G^2, G^3, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} will be explained.

As a halogen atom, fluorine, chlorine, bromine or iodine may be mentioned.

A C_{1-3} alkyl group may be linear, branched or a C_3 cycloalkyl group, and methyl, ethyl, n-propyl, i-propyl and c-propyl and the like may be mentioned. A C_{1-6} alkyl group may be linear, branched or a C_{3-6} cycloalkyl group, and in addition to those mentioned above, n-butyl, i-butyl, s-butyl, t-butyl, c-butyl, 1-methyl-c-propyl, 2-methyl-c-propyl, n-pentyl, 1-methyl-n-butyl, 2-methyl-n-butyl, 3-methyl-n-butyl, 1,1-dimethyl-n-propyl, 1,2-dimethyl-n-propyl, 2,2-dimethyl-n-propyl, 1-ethyl-n-propyl, c-pentyl, 1-methyl-c-butyl, 2-methyl-c-butyl, 3-methyl-c-butyl, 1,2-dimethyl-c-propyl, 2,3-dimethyl-c-propyl, 1-ethyl-c-propyl, 2-ethyl-c-propyl, n-hexyl, 1-methyl-n-pentyl, 2-methyl-n-pentyl, 3-methyl-n-pentyl, 4-methyl-n-pentyl, 1,1-dimethyl-n-butyl, 1,2-dimethyl-n-butyl, 1,3-dimethyl-n-butyl, 2,2-dimethyl-n-butyl, 2,3-dimethyl-n-butyl, 3,3-dimethyl-n-butyl, 1-ethyl-n-butyl, 2-ethyl-n-butyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 1-ethyl-1-methyl-n-propyl, 1-ethyl-2-methyl-n-propyl, c-hexyl, 1-methyl-c-pentyl, 2-methyl-c-pentyl, 3-methyl-c-pentyl, 1-ethyl-c-butyl, 2-ethyl-c-butyl, 3-ethyl-c-butyl, 1,2-dimethyl-c-butyl, 1,3-dimethyl-c-butyl, 2,2-dimethyl-c-butyl, 2,3-dimethyl-c-butyl, 2,4-dimethyl-c-butyl, 3,3-dimethyl-c-butyl, 1-n-propyl-c-propyl, 2-n-propyl-c-propyl, 1-i-propyl-c-propyl, 2-i-propyl-c-propyl, 1,2,2-trimethyl-c-propyl, 1,2,3-trimethyl-c-propyl, 2,2,3-trimethyl-c-propyl, 1-ethyl-2-methyl-c-propyl, 2-ethyl-1-methyl-c-propyl, 2-

ethyl-2-methyl-c-propyl, 2-ethyl-3-methyl-c-propyl and the like may be mentioned.

A C_{2-14} aryl group may be a C_{6-14} aryl group containing no hetero atoms as ring constituting atoms or a C_{2-9} aromatic heterocyclic group, and a C_{2-9} aromatic heterocyclic group may be a 5 to 7-membered C_{2-6} heteromonocyclic group or 8 to 10-membered C_{5-9} fused heterobicyclic group containing from 1 to 3 oxygen atoms, nitrogen atoms or sulfur atoms singly or in combination.

As a C_{6-14} aryl group containing no hetero atoms, a phenyl group, a 1-indenyl group, a 2-indenyl group, a 3-indenyl group, a 4-indenyl group, a 5-indenyl group, a 6-indenyl group, a 7-indenyl group, an α-naphthyl group, a β-naphthyl group, a 1-tetrahydronaphthyl group, a 2-tetrahydronaphthyl group, a 5-tetrahydronaphthyl group, a 6-tetrahydronaphthyl group, an o-biphenyl group, a m-biphenyl group, a p-biphenyl group, a 1-anthryl group, a 2-anthryl group, a 9-anthryl group, a 1-phenanthryl group, a 2-phenanthryl group, a 3-phenanthryl group, a 4-phenanthryl group, a 9-phenanthryl group or the like may be mentioned.

A 5 to 7-membered C_{2-6} heteromonocyclic group may be a 2-thienyl group, a 3-thienyl group, a 2-furyl group, a 3-furyl group, a 2-pyranyl group, a 3-pyranyl group, a 4-pyranyl group, a 1-pyrrolyl group, a 2-pyrrolyl group, a 3-pyrrolyl group, a 1-imidazolyl group, a 2-imidazolyl group, a 4-imidazolyl group, a 1-pyrazolyl group, a 3-

pyrazolyl group, a 4-pyrazolyl group, a 2-thiazolyl group, a 4-thiazolyl group, a 5-thiazolyl group, a 3-isothiazolyl group, a 4-isothiazolyl group, a 5-isothiazolyl group, a 2-oxazolyl group, a 4-oxazolyl group, a 5-oxazolyl group, a 3-isoxazolyl group, a 4-isoxazolyl group, a 5-isoxazolyl group, a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group, a 2-pyrazinyl group, a 2-pyrimidinyl group, a 4-pyrimidinyl group, a 5-pyrimidinyl group, a 3-pyridazinyl group, a 4-pyridazinyl group, a 2-1,3,4-oxadiazolyl group, a 2-1,3,4-thiadiazolyl group, a 3-1,2,4-oxadiazolyl group, a 5-1,2,4-oxadiazolyl group, a 3-1,2,4-thiadiazolyl group, a 5-1,2,4-thiadiazolyl group, a 3-1,2,5-oxadiazolyl group, a 3-1,2,5-thiadiazolyl group or the like.

A 8 to 10-membered C_{5-9} fused heterocyclic group may be a 2-benzofuranyl group, a 3-benzofuranyl group, a 4-benzofuranyl group, a 5-benzofuranyl group, a 6-benzofuranyl group, a 7-benzofuranyl group, a 1-isobenzofuranyl group, a 4-isobenzofuranyl group, a 5-isobenzofuranyl group, a 2-benzothienyl group, a 3-benzothienyl group, a 4-benzothienyl group, a 5-benzothienyl group, a 6-benzothienyl group, a 7-benzothienyl group, a 1-isobenzothienyl group, a 4-isobenzothienyl group, a 5-isobenzothienyl group, a 2-chromenyl group, a 3-chromenyl group, a 4-chromenyl group, a 5-chromenyl group, a 6-chromenyl group, a 7-chromenyl group, a 8-chromenyl group, a 1-indolizinyl

group, a 2-indolizinyl group, a 3-indolizinyl group, a 5-indolizinyl group, a 6-indolizinyl group, a 7-indolizinyl group, a 8-indolizinyl group, a 1-isoindolyl group, a 2-isoindolyl group, a 4-isoindolyl group, a 5-isoindolyl group, a 1-indolyl group, a 2-indolyl group, a 3-indolyl group, a 4-indolyl group, a 5-indolyl group, a 6-indolyl group, a 7-indolyl group, 1-indazolyl group, a 2-indazolyl group, a 3-indazolyl group, a 4-indazolyl group, a 5-indazolyl group, a 6-indazolyl group, a 7-indazolyl group, a 1-purinyl group, a 2-purinyl group, a 3-purinyl group, a 6-purinyl group, a 7-purinyl group, a 8-purinyl group, a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinolyl group, a 8-quinolyl group, a 1-isoquinolyl group, a 3-isoquinolyl group, a 4-isoquinolyl group, a 5-isoquinolyl group, a 6-isoquinolyl group, a 7-isoquinolyl group, a 8-isoquinolyl group, a 1-phthalazinyl group, a 5-phthalazinyl group, a 6-phthalazinyl group, a 1-2,7-naphthyridinyl group, a 3-2,7-naphthyridinyl group, a 4-2,7-naphthyridinyl group, a 1-2,6-naphthyridinyl group, a 3-2,6-naphthyridinyl group, a 4-2,6-naphthyridinyl group, a 2-1,8-naphthyridinyl group, a 3-1,8-naphthyridinyl group, a 4-1,8-naphthyridinyl group, a 2-1,7-naphthyridinyl group, a 3-1,7-naphthyridinyl group, a 4-1,7-naphthyridinyl group, a 5-1,7-naphthyridinyl group, a 6-1,7-naphthyridinyl group, a 8-1,7-naphthyridinyl group, 2-1,6-naphthyridinyl group,

a 3-1,6-naphthyridinyl group, a 4-1,6-naphthyridinyl group, a 5-1,6-naphthyridinyl group, a 7-1,6-naphthyridinyl group, a 8-1,6-naphthyridinyl group, a 2-1,5-naphthyridinyl group, a 3-1,5-naphthyridinyl group, a 4-1,5-naphthyridinyl group, a 6-1,5-naphthyridinyl group, a 7-1,5-naphthyridinyl group, a 8-1,5-naphthyridinyl group, a 2-quinoxalinyl group, a 5-quinoxalinyl group, a 6-quinoxalinyl group, a 2-quinazolinyl group, a 4-quinazolinyl group, a 5-quinazolinyl group, a 6-quinazolinyl group, a 7-quinazolinyl group, a 8-quinazolinyl group, a 3-cinnolinyl group, a 4-cinnolinyl group, a 5-cinnolinyl group, a 6-cinnolinyl group, a 7-cinnolinyl group, a 8-cinnolinyl group, a 2-pterdinyl group, a 4-pterdinyl group, a 6-pterdinyl group, a 7-pterdinyl group or the like.

A C_{1-3} alkyl group substituted with one or more fluorine atoms may be a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a pentafluoroethyl group, a 1,1-difluoro-2,2-difluoroethyl group, a heptafluoropropyl group or the like.

A C_{1-6} alkylcarbonyl group may be methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl, n-butylcarbonyl, i-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, n-pentylcarbonyl, 1-methyl-n-butylcarbonyl, 2-methyl-n-butylcarbonyl, 3-methyl-n-butylcarbonyl, 1,1-dimethyl-n-propylcarbonyl, 1,2-dimethyl-n-propylcarbonyl, 2,2-dimethyl-n-propylcarbonyl,

1-ethyl-n-propylcarbonyl, n-hexylcarbonyl, 1-methyl-n-pentylcarbonyl, 2-methyl-n-pentylcarbonyl, 3-methyl-n-pentylcarbonyl, 4-methyl-n-pentylcarbonyl, 1,1-dimethyl-n-butylcarbonyl, 1,2-dimethyl-n-butylcarbonyl, 1,3-dimethyl-n-butylcarbonyl, 2,2-dimethyl-n-butylcarbonyl, 2,3-dimethyl-n-butylcarbonyl, 3,3-dimethyl-n-butylcarbonyl, 1-ethyl-n-butylcarbonyl, 2-ethyl-n-butylcarbonyl, 1,1,2-trimethyl-n-propylcarbonyl, 1,2,2-trimethyl-n-propylcarbonyl, 1-ethyl-1-methyl-n-propylcarbonyl, 1-ethyl-2-methyl-n-propylcarbonyl or the like.

A C_{1-6} alkoxycarbonyl group may be methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl, n-pentyloxycarbonyl, 1-methyl-n-butoxycarbonyl, 2-methyl-n-butoxycarbonyl, 3-methyl-n-butoxycarbonyl, 1,1-dimethyl-n-propoxycarbonyl, 1,2-dimethyl-n-propoxycarbonyl, 2,2-dimethyl-n-propoxycarbonyl, 1-ethyl-n-propoxycarbonyl, n-hexyloxycarbonyl, 1-methyl-n-pentyloxycarbonyl, 2-methyl-n-pentyloxycarbonyl, 3-methyl-n-pentyloxycarbonyl, 4-methyl-n-pentyloxycarbonyl, 1,1-dimethyl-n-butoxycarbonyl, 1,2-dimethyl-n-butoxycarbonyl, 1,3-dimethyl-n-butoxycarbonyl, 2,2-dimethyl-n-butoxycarbonyl, 2,3-dimethyl-n-butoxycarbonyl, 3,3-dimethyl-n-butoxycarbonyl, 1-ethyl-n-butoxycarbonyl, 2-ethyl-n-butoxycarbonyl, 1,1,2-trimethyl-n-propoxycarbonyl, 1,2,2-

trimethyl-n-propoxycarbonyl, 1-ethyl-1-methyl-n-propoxycarbonyl, 1-ethyl-2-methyl-n-propoxycarbonyl or the like.

Specific preferred examples of the substituents A, R^1, R^7 and R^{12} are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group), pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group), quinolyl groups (a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinolyl group and a 8-quinolyl group) and isoquinolyl groups (a 1-isoquinolyl group, a 3-isoquinolyl group, a 4-isoquinolyl group, a 5-isoquinolyl group, a 6-isoquinolyl group, a 7-isoquinolyl group and a 8-isoquinolyl group) optionally substituted with one or more of the following substituents.

Substituents: a C_{1-6} alkyl group, a halogen atom, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a nitro group, an amino group, an amino group substituted with a C_{1-6} alkyl group, an amino group substituted with a C_{1-6} alkylcarbonyl group, a hydroxyl group, a hydroxyl group substituted with a C_{1-6} alkyl group, a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group and a C_{1-6} alkylcarbonyl group.

Particularly preferred examples of the substituents A, R^1, R^7 and R^{12} are a phenyl group, thienyl groups (a 2-

thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group) and pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group) optionally substituted with one or more of the following substituents.

Substituents: a C_{1-6} alkyl group, a halogen atom, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a nitro group, an amino group, an amino group substituted with a C_{1-6} alkyl group, an amino group substituted with an C_{1-6} alkylcarbonyl group, a hydroxyl group, a hydroxyl group substituted with a C_{1-6} alkyl group, a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group and a C_{1-6} alkylcarbonyl group.

Still further preferred specific examples of the substituents A, R^1, R^7 and R^{12} are a 3-methyl-phenyl group, a 4-methyl-phenyl group, a 3,4-dimethyl-phenyl group, a 3-t-butyl-phenyl group, a 4-t-butyl-phenyl group, a 3-trifluoromethyl-phenyl group, a 4-trifluoromethyl-phenyl group, a 3,4-ditrifluoromethyl-phenyl group, a 3-chloro-phenyl group, a 4-chloro-phenyl group, a 3-iodo-phenyl group, a 4-iodo-phenyl group, a 3-fluoro-phenyl group, a 4-fluoro-phenyl group, a 3,4-dichloro-phenyl group, a 3,4-diiode-phenyl group, a 3,4-difluoro-phenyl group, a 3-nitro-phenyl group, a 4-nitro-phenyl group, a α-naphthyl group, a β-naphthyl group and the like.

Specific preferable examples of the substituents B, R^2, R^8 and R^{13} are a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a trifluoromethyl group and a phenyl group, and particularly preferred examples are a methyl group, an ethyl group and a trifluoromethyl group.

Specific preferable examples of the substituents D, R^3, R^9 and R^{14} are a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a c-propyl group and a phenyl group, and particularly preferable examples are a hydrogen atom, a methyl group and an ethyl group.

Specific preferable examples of the substituent R^4 are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group), pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group), quinolyl groups (a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinolyl group and a 8-quinolyl group) and isoquinolyl groups (a 1-isoquinolyl group, a 3-isoquinolyl group, a 4-isoquinolyl group, a 5-isoquinolyl group, a 6-isoquinolyl group, a 7-isoquinolyl group and a 8-isoquinolyl group) substituted with one or more of the following substituents.

Substituents: a hydroxyl group, an amino group and a

nitro group.

Specific particularly preferred examples of the substituent R^4 are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group) and pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group) substituted with one or more of the following substituents.

Substituents: a hydroxyl group, an amino group and a nitro group.

Specific preferable example of the substituent R^{10} are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group), pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group), quinolyl groups (a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinoyl group and a 8-quinolyl group) and isoquinolyl groups (a 1-isoquinolyl group, a 3-isoquinolyl group, a 4-isoquinolyl group, a 5-isoquinolyl group, a 6-isoquinolyl group, a 7-isoquinolyl group and a 8-isoquinolyl group) substituted with one or more of the following substituents.

Substituents: a carboxyl group, sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido

group, a hydroxycarbamido group, a hydroxysulfamido group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$, $CH_2CH_2CO_2H$ and a tetrazole group.

Specific particularly preferred examples of the substituent R^{10} are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group) and pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group) substituted with one or more of the following substituents.

Substituents: a carboxyl group, a sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido group, a hydroxycarbamido group, a hydroxysulfamido group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$, $CH_2CH_2CO_2H$ and a tetrazole group.

Specific preferable examples of the substituent R^{15} are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group), pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group), quinolyl groups (a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinolyl group and a 8-quinolyl group) and isoquinolyl groups (a 1-isoquinolyl group, a 3-isoquinolyl group, a 4-isoquinolyl group, a 5-isoquinolyl group, a 6-

isoquinolyl group, a 7-isoquinolyl group and a 8-isoquinolyl group) substituted with a substituent selected from a hydroxyl group and an amino group and with a substituent selected from the following substituents.

Substituents: a carboxyl group, a sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido group, a hydroxycarbamido group, a hydroxysulfamido group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$, $CH_2CH_2CO_2H$ and a tetrazole group.

Specific particularly preferred examples of the substituent R^{15} are a phenyl group, thienyl groups (a 2-thienyl group and a 3-thienyl group), furyl groups (a 2-furyl group and a 3-furyl group), pyridazinyl groups (a 3-pyridazinyl group and a 4-pyridazinyl group) and pyridyl groups (a 2-pyridyl group, a 3-pyridyl group and a 4-pyridyl group) substituted with a substituent selected from a hydroxyl group and an amino group and with a substituent selected from the following substituents.

Substituents: a carboxyl group, a sulfonic acid group, a phosphonic acid group, a carbamido group, a sulfamido group, a hydroxycarbamido group, a hydroxysulfamido group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$, $CH_2CH_2CO_2H$ and a tetrazole group.

Favorable compounds as the thrombopoietin receptor activator, the preventive, therapeutic or improving agent

for diseases against which activation of the thrombopoietin receptor is effective and the platelet increasing agent of the present invention are as follows.

1) Pyrazolone compounds represented by the formula (2) wherein R^4 is a C_{2-14} aryl group substituted with one or more hydroxyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

2) Pyrazolone compounds represented by the formula (2) wherein R^4 is a C_{2-14} aryl group substituted with NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

3) Pyrazolone compounds represented by the formula (2) wherein R^4 is a phenyl group or pyridyl group substituted with one or more hydroxyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

4) Pyrazolone compounds represented by the formula (2) wherein R^4 is a phenyl group or pyridyl group substituted with NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

5) Pyrazolone compounds represented by the formula (2)

wherein R^4 is a thienyl group, furyl group or pyridazinyl group substituted with one or more hydroxyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

6) Pyrazolone compounds represented by the formula (2) wherein R^4 is a thienyl, furyl group or pyridazinyl group substituted with NR^5R^6 (wherein R^5 and R^6 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

7) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1,2 or 3), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

8) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1,2 or 3), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

9) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or a pyridazinyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{11} (R^{11} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

10) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

11) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

12) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

13) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a sulfonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or

solvates thereof.

14) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a sulfonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

15) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a sulfonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

16) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a phosphonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

17) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a phosphonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

18) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a phosphonic acid group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

19) Pyrazolone compounds represented by the formula (3)

wherein R^{10} is a C_{2-14} aryl group substituted with a carbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

20) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a carbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

21) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a carbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

22) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a sulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

23) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a sulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

24) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a sulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

25) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a hydroxycarbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

26) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a hydroxycarbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

27) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxycarbamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

28) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a hydroxysulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

29) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a hydroxysulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

30) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or

pyridazinyl group substituted with a hydroxysulfamido group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

31) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a C_{2-14} aryl group substituted with a tetrazole group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

32) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a phenyl group or pyridyl group substituted with a tetrazole group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

33) Pyrazolone compounds represented by the formula (3) wherein R^{10} is a thienyl group, furyl group or pyridazinyl group substituted with a tetrazole group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

34) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a C_{2-14} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with a hydroxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

35) Pyrazolone compounds represented by the formula (4)

wherein R^{15} is a phenyl or pyridyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with a hydroxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

36) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a thienyl group, furyl group or pyridazinyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with a hydroxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

37) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a C_{2-14} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with an amino group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

38) Pyrazolone compounds represented by the formula (4)

wherein R^{15} is a phenyl or pyridyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with an amino group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

39) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a thienyl group, furyl group or pyridazinyl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^{16} (R^{16} is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with an amino group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

40) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a C_{2-14} aryl group substituted with a substituent selected from a hydroxyl group, an amino group, a nitro group and a halogen atom and with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

41) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a phenyl or pyridyl group substituted with a substituent selected from a hydroxyl group, an amino group, a nitro group and a halogen atom and with a

carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

42) Pyrazolone compounds represented by the formula (4) wherein R^{15} is a thienyl group, furyl group or pyridazinyl group substituted with a substituent selected from a hydroxyl group, an amino group, a nitro group and a halogen atom and with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

43) The pyrazolone compounds according to 1), 2), 3), 4), 5) or 6), wherein R^2 is a C_{1-3} alkyl group substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

44) The pyrazolone compounds according to 1), 2), 3), 4), 5) or 6), wherein R^2 is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

45) The pyrazolone compounds according to 1), 2), 3), 4), 5) or 6), wherein R^2 is hydrogen, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

46) The pyrazolone compounds according to 7), 8), 9), 10), 11), 12), 13) 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32) or 33), wherein R^8 is a C_{1-3} alkyl group substituted with one or more fluorine atoms, tautomers, prodrugs or

pharmaceutically acceptable salts of the compounds or solvates thereof.

47) The pyrazolone compounds according to 7), 8), 9), 10), 11), 12), 13) 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32) or 33), wherein R^8 is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

48) The pyrazolone compounds according to 7), 8), 9), 10), 11), 12), 13) 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32) or 33), wherein R^8 is hydrogen, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

49) The pyrazolone compounds according to 34), 35), 36), 37), 38), 39), 40), 41) or 42), wherein R^{13} is a C_{1-3} alkyl group substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

50) The pyrazolone compounds according to 34), 35), 36), 37), 38), 39), 40), 41) or 42), wherein R^{13} is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

51) The pyrazolone compounds according to 34), 35), 36), 37), 38), 39), 40), 41) or 42), wherein R^{13} is hydrogen, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

52) The pyrazolone compounds according to 1), 2), 3), 4), 5), 6), 43), 44) or 45), wherein R^3 is a hydrogen atom, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

53) The pyrazolone compounds according to 1), 2), 3), 4), 5), 6), 43), 44) or 45), wherein R^3 is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

54) The pyrazolone compounds according to 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32), 33), 46), 47) or 48), wherein R^9 is a hydrogen atom, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

55) The pyrazolone compounds according to 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32), 33), 46), 47) or 48), wherein R^9 is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

56) The pyrazolone compounds according to 34), 35), 36), 37), 38), 39), 40), 41), 42), 49), 50) or 51), wherein R^{14} is a hydrogen atom, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

57) The pyrazolone compounds according to 34), 35), 36), 37), 38), 39), 40), 41), 42), 49), 50) or 51), wherein

R^{14} is a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

58) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

59) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

60) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

61) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

62) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or

solvates thereof.

63) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

64) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

65) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

66) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

67) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

68) The pyrazolone compounds according to 52) or 53),

wherein R^1 is a phenyl group or pyridyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

69) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

70) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

71) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

72) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

73) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with one or more halogen atoms, tautomers, prodrugs or

pharmaceutically acceptable salts of the compounds or solvates thereof.

74) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

75) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

76) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

77) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

78) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers,

prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

79) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

80) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

81) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

82) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

83) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with one or more C_{1-3} alkyl groups substituted

with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

84) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

85) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

86) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

87) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

88) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with a

hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

89) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

90) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

91) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

92) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

93) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group

substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

94) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

95) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

96) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

97) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

98) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts

of the compounds or solvates thereof.

99) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

100) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

101) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

102) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

103) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

104) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

105) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

106) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

107) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

108) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or

pharmaceutically acceptable salts of the compounds or solvates thereof.

109) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

110) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

111) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

112) The pyrazolone compounds according to 52) or 53), wherein R^{1} is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

113) The pyrazolone compounds according to 52) or 53), wherein R^{1} is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl

group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

114) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

115) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

116) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

117) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

118) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group,

tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

119) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

120) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

121) The pyrazolone compounds according to 52) or 53), wherein R^1 is a C_{2-14} aryl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

122) The pyrazolone compounds according to 52) or 53), wherein R^1 is a phenyl group or pyridyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

123) The pyrazolone compounds according to 52) or 53), wherein R^1 is a thienyl group, furyl group or pyridazinyl group substituted with a C_{1-6} alkylcarbonyl group,

tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

124) The pyrazolone compounds according to 54) or 55), wherein R^7 is a C_{2-14} aryl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

125) The pyrazolone compounds according to 54) or 55), wherein R^7 is a phenyl group or pyridyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

126) The pyrazolone compounds according to 54) or 55), wherein R^7 is a thienyl group, furyl group or pyridazinyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

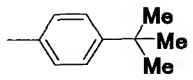
127) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a C_{2-14} aryl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

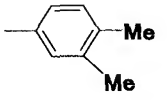
128) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a phenyl group or pyridyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

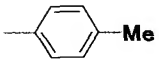
129) The pyrazolone compounds according to 56) or 57), wherein R^{12} is a thienyl group, furyl group or pyridazinyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

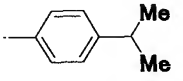
130) The compounds wherein R^7, R^8, R^9 and R^{10} are any of the following combinations in Table 1, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof. The symbols in Table 1 denote the following substituents.

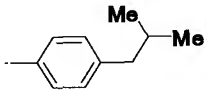
【Ka 9】

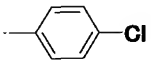
Q1a = 

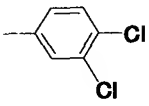
Q1b = 

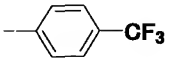
Q1c = 

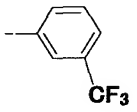
Q1d = 

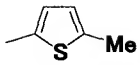
Q1e = 

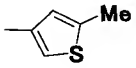
Q1f = 

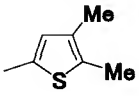
Q1g = 

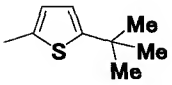
Q1h = 

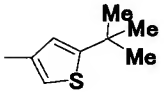
Q1i = 

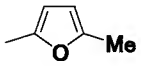
Q1j = 

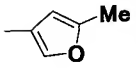
Q1k= 

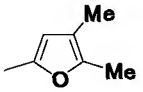
Q1l = 

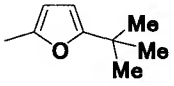
Q1m = 

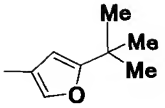
Q1n = 

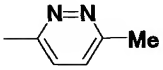
Q1o = 

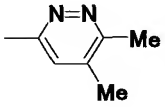
Q1p= 

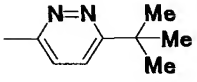
Q1q= 

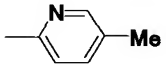
Q1r= 

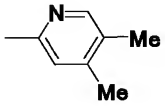
Q1s= 

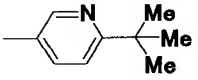
Q1t= 

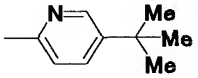
Q1u = 

Q1v= 

Q1w= 

Q1x= 

Q1y= 

Q1z= 

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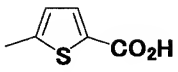
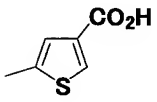
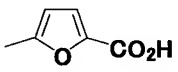
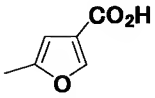
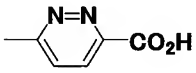
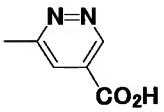
Q3a = 

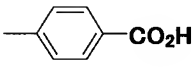
Q3b = 

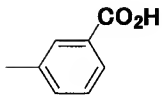
Q3c = 

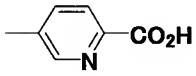
Q3d = 

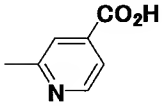
Q3e = 

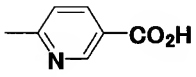
Q3f= 

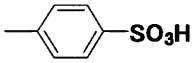
Q3g= 

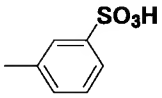
Q3h= 

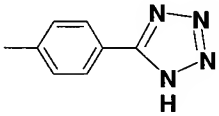
Q3i= 

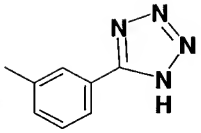
Q3j= 

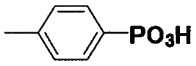
Q3k= 

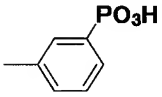
Q3l = 

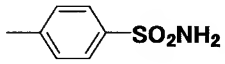
Q3m = 

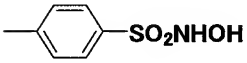
Q3n= 

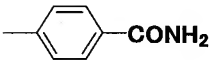
Q3o= 

Q3p= 

Q3q = 

Q3r= 

Q3s= 

Q3t = 

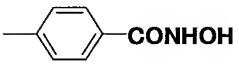
Q3u= 

Table 1

No	R^7	R^8	R^9	R^{10}
1	Q1a	H	H	Q3a
2	Q1a	H	H	Q3b
3	Q1a	H	H	Q3c
4	Q1a	H	H	Q3d
5	Q1a	H	H	Q3e
6	Q1a	H	H	Q3f
7	Q1a	H	H	Q3g
8	Q1a	H	H	Q3h
9	Q1a	H	H	Q3i
10	Q1a	H	H	Q3j
11	Q1a	H	H	Q3k
12	Q1a	H	H	Q3l
13	Q1a	H	H	Q3m
14	Q1a	H	H	Q3n
15	Q1a	H	H	Q3o
16	Q1a	H	H	Q3p
17	Q1a	H	H	Q3q
18	Q1a	H	Me	Q3a
19	Q1a	H	Me	Q3b
20	Q1a	H	Me	Q3c
21	Q1a	H	Me	Q3d
22	Q1a	H	Me	Q3e
23	Q1a	H	Me	Q3f
24	Q1a	H	Me	Q3g
25	Q1a	H	Me	Q3h
26	Q1a	H	Me	Q3i
27	Q1a	H	Me	Q3j
28	Q1a	H	Me	Q3k
29	Q1a	H	Me	Q3l
30	Q1a	H	Me	Q3m
31	Q1a	H	Me	Q3n
32	Q1a	H	Me	Q3o
33	Q1a	H	Me	Q3p
34	Q1a	H	Me	Q3q
35	Q1a	Me	H	Q3a
36	Q1a	Me	H	Q3b
37	Q1a	Me	H	Q3c
38	Q1a	Me	H	Q3d
39	Q1a	Me	H	Q3e
40	Q1a	Me	H	Q3f
41	Q1a	Me	H	Q3g
42	Q1a	Me	H	Q3h
43	Q1a	Me	H	Q3i

44	Q1a	Me	H	Q3j
45	Q1a	Me	H	Q3k
46	Q1a	Me	H	Q3l
47	Q1a	Me	H	Q3m
48	Q1a	Me	H	Q3n
49	Q1a	Me	H	Q3o
50	Q1a	Me	H	Q3p
51	Q1a	Me	H	Q3q
52	Q1a	Me	Me	Q3a
53	Q1a	Me	Me	Q3b
54	Q1a	Me	Me	Q3c
55	Q1a	Me	Me	Q3d
56	Q1a	Me	Me	Q3e
57	Q1a	Me	Me	Q3f
58	Q1a	Me	Me	Q3g
59	Q1a	Me	Me	Q3h
60	Q1a	Me	Me	Q3i
61	Q1a	Me	Me	Q3j
62	Q1a	Me	Me	Q3k
63	Q1a	Me	Me	Q3l
64	Q1a	Me	Me	Q3m
65	Q1a	Me	Me	Q3n
66	Q1a	Me	Me	Q3o
67	Q1a	Me	Me	Q3p
68	Q1a	Me	Me	Q3q
69	Q1a	CF3	H	Q3a
70	Q1a	CF3	H	Q3b
71	Q1a	CF3	H	Q3c
72	Q1a	CF3	H	Q3d
73	Q1a	CF3	H	Q3e
74	Q1a	CF3	H	Q3f
75	Q1a	CF3	H	Q3g
76	Q1a	CF3	H	Q3h
77	Q1a	CF3	H	Q3i
78	Q1a	CF3	H	Q3j
79	Q1a	CF3	H	Q3k
80	Q1a	CF3	H	Q3l
81	Q1a	CF3	H	Q3m
82	Q1a	CF3	H	Q3n
83	Q1a	CF3	H	Q3o
84	Q1a	CF3	H	Q3p
85	Q1a	CF3	H	Q3q
86	Q1a	CF3	Me	Q3a
87	Q1a	CF3	Me	Q3b
88	Q1a	CF3	Me	Q3c

89	Q1a	CF3	Me	Q3d
90	Q1a	CF3	Me	Q3e
91	Q1a	CF3	Me	Q3f
92	Q1a	CF3	Me	Q3g
93	Q1a	CF3	Me	Q3h
94	Q1a	CF3	Me	Q3i
95	Q1a	CF3	Me	Q3j
96	Q1a	CF3	Me	Q3k
97	Q1a	CF3	Me	Q3l
98	Q1a	CF3	Me	Q3m
99	Q1a	CF3	Me	Q3n
100	Q1a	CF3	Me	Q3o
101	Q1a	CF3	Me	Q3p
102	Q1a	CF3	Me	Q3q
103	Q1b	H	H	Q3a
104	Q1b	H	H	Q3b
105	Q1b	H	H	Q3c
106	Q1b	H	H	Q3d
107	Q1b	H	H	Q3e
108	Q1b	H	H	Q3f
109	Q1b	H	H	Q3g
110	Q1b	H	H	Q3h
111	Q1b	H	H	Q3i
112	Q1b	H	H	Q3j
113	Q1b	H	H	Q3k
114	Q1b	H	H	Q3l
115	Q1b	H	H	Q3m
116	Q1b	H	H	Q3n
117	Q1b	H	H	Q3o
118	Q1b	H	H	Q3p
119	Q1b	H	H	Q3q
120	Q1b	H	Me	Q3a
121	Q1b	H	Me	Q3b
122	Q1b	H	Me	Q3c
123	Q1b	H	Me	Q3d
124	Q1b	H	Me	Q3e
125	Q1b	H	Me	Q3f
126	Q1b	H	Me	Q3g
127	Q1b	H	Me	Q3h
128	Q1b	H	Me	Q3i
129	Q1b	H	Me	Q3j
130	Q1b	H	Me	Q3k
131	Q1b	H	Me	Q3l
132	Q1b	H	Me	Q3m
133	Q1b	H	Me	Q3n

134	Q1b	H	Me	Q3o
135	Q1b	H	Me	Q3p
136	Q1b	H	Me	Q3q
137	Q1b	Me	H	Q3a
138	Q1b	Me	H	Q3b
139	Q1b	Me	H	Q3c
140	Q1b	Me	H	Q3d
141	Q1b	Me	H	Q3e
142	Q1b	Me	H	Q3f
143	Q1b	Me	H	Q3g
144	Q1b	Me	H	Q3h
145	Q1b	Me	H	Q3i
146	Q1b	Me	H	Q3j
147	Q1b	Me	H	Q3k
148	Q1b	Me	H	Q3l
149	Q1b	Me	H	Q3m
150	Q1b	Me	H	Q3n
151	Q1b	Me	H	Q3o
152	Q1b	Me	H	Q3p
153	Q1b	Me	H	Q3q
154	Q1b	Me	Me	Q3a
155	Q1b	Me	Me	Q3b
156	Q1b	Me	Me	Q3c
157	Q1b	Me	Me	Q3d
158	Q1b	Me	Me	Q3e
159	Q1b	Me	Me	Q3f
160	Q1b	Me	Me	Q3g
161	Q1b	Me	Me	Q3h
162	Q1b	Me	Me	Q3i
163	Q1b	Me	Me	Q3j
164	Q1b	Me	Me	Q3k
165	Q1b	Me	Me	Q3l
166	Q1b	Me	Me	Q3m
167	Q1b	Me	Me	Q3n
168	Q1b	Me	Me	Q3o
169	Q1b	Me	Me	Q3p
170	Q1b	Me	Me	Q3q
171	Q1b	CF3	H	Q3a
172	Q1b	CF3	H	Q3b
173	Q1b	CF3	H	Q3c
174	Q1b	CF3	H	Q3d
175	Q1b	CF3	H	Q3e
176	Q1b	CF3	H	Q3f
177	Q1b	CF3	H	Q3g
178	Q1b	CF3	H	Q3h

179	Q1b	CF3	H	Q3i
180	Q1b	CF3	H	Q3j
181	Q1b	CF3	H	Q3k
182	Q1b	CF3	H	Q3l
183	Q1b	CF3	H	Q3m
184	Q1b	CF3	H	Q3n
185	Q1b	CF3	H	Q3o
186	Q1b	CF3	H	Q3p
187	Q1b	CF3	H	Q3q
188	Q1b	CF3	Me	Q3a
189	Q1b	CF3	Me	Q3b
190	Q1b	CF3	Me	Q3c
191	Q1b	CF3	Me	Q3d
192	Q1b	CF3	Me	Q3e
193	Q1b	CF3	Me	Q3f
194	Q1b	CF3	Me	Q3g
195	Q1b	CF3	Me	Q3h
196	Q1b	CF3	Me	Q3i
197	Q1b	CF3	Me	Q3j
198	Q1b	CF3	Me	Q3k
199	Q1b	CF3	Me	Q3l
200	Q1b	CF3	Me	Q3m
201	Q1b	CF3	Me	Q3n
202	Q1b	CF3	Me	Q3o
203	Q1b	CF3	Me	Q3p
204	Q1b	CF3	Me	Q3q
205	Q1c	H	H	Q3a
206	Q1c	H	H	Q3b
207	Q1c	H	H	Q3c
208	Q1c	H	H	Q3d
209	Q1c	H	H	Q3e
210	Q1c	H	H	Q3f
211	Q1c	H	H	Q3g
212	Q1c	H	H	Q3h
213	Q1c	H	H	Q3i
214	Q1c	H	H	Q3j
215	Q1c	H	H	Q3k
216	Q1c	H	H	Q3l
217	Q1c	H	H	Q3m
218	Q1c	H	H	Q3n
219	Q1c	H	H	Q3o
220	Q1c	H	H	Q3p
221	Q1c	H	H	Q3q
222	Q1c	H	Me	Q3a
223	Q1c	H	Me	Q3b

224	Q1c	H	Me	Q3c
225	Q1c	H	Me	Q3d
226	Q1c	H	Me	Q3e
227	Q1c	H	Me	Q3f
228	Q1c	H	Me	Q3g
229	Q1c	H	Me	Q3h
230	Q1c	H	Me	Q3i
231	Q1c	H	Me	Q3j
232	Q1c	H	Me	Q3k
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234	Q1c	H	Me	Q3m
235	Q1c	H	Me	Q3n
236	Q1c	H	Me	Q3o
237	Q1c	H	Me	Q3p
238	Q1c	H	Me	Q3q
239	Q1c	Me	H	Q3a
240	Q1c	Me	H	Q3b
241	Q1c	Me	H	Q3c
242	Q1c	Me	H	Q3d
243	Q1c	Me	H	Q3e
244	Q1c	Me	H	Q3f
245	Q1c	Me	H	Q3g
246	Q1c	Me	H	Q3h
247	Q1c	Me	H	Q3i
248	Q1c	Me	H	Q3j
249	Q1c	Me	H	Q3k
250	Q1c	Me	H	Q3l
251	Q1c	Me	H	Q3m
252	Q1c	Me	H	Q3n
253	Q1c	Me	H	Q3o
254	Q1c	Me	H	Q3p
255	Q1c	Me	H	Q3q
256	Q1c	Me	Me	Q3a
257	Q1c	Me	Me	Q3b
258	Q1c	Me	Me	Q3c
259	Q1c	Me	Me	Q3d
260	Q1c	Me	Me	Q3e
261	Q1c	Me	Me	Q3f
262	Q1c	Me	Me	Q3g
263	Q1c	Me	Me	Q3h
264	Q1c	Me	Me	Q3i
265	Q1c	Me	Me	Q3j
266	Q1c	Me	Me	Q3k
267	Q1c	Me	Me	Q3l
268	Q1c	Me	Me	Q3m

269	Q1c	Me	Me	Q3n
270	Q1c	Me	Me	Q3o
271	Q1c	Me	Me	Q3p
272	Q1c	Me	Me	Q3q
273	Q1c	CF3	H	Q3a
274	Q1c	CF3	H	Q3b
275	Q1c	CF3	H	Q3c
276	Q1c	CF3	H	Q3d
277	Q1c	CF3	H	Q3e
278	Q1c	CF3	H	Q3f
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280	Q1c	CF3	H	Q3h
281	Q1c	CF3	H	Q3i
282	Q1c	CF3	H	Q3j
283	Q1c	CF3	H	Q3k
284	Q1c	CF3	H	Q3l
285	Q1c	CF3	H	Q3m
286	Q1c	CF3	H	Q3n
287	Q1c	CF3	H	Q3o
288	Q1c	CF3	H	Q3p
289	Q1c	CF3	H	Q3q
290	Q1c	CF3	Me	Q3a
291	Q1c	CF3	Me	Q3b
292	Q1c	CF3	Me	Q3c
293	Q1c	CF3	Me	Q3d
294	Q1c	CF3	Me	Q3e
295	Q1c	CF3	Me	Q3f
296	Q1c	CF3	Me	Q3g
297	Q1c	CF3	Me	Q3h
298	Q1c	CF3	Me	Q3i
299	Q1c	CF3	Me	Q3j
300	Q1c	CF3	Me	Q3k
301	Q1c	CF3	Me	Q3l
302	Q1c	CF3	Me	Q3m
303	Q1c	CF3	Me	Q3n
304	Q1c	CF3	Me	Q3o
305	Q1c	CF3	Me	Q3p
306	Q1c	CF3	Me	Q3q
307	Q1d	H	H	Q3a
308	Q1d	H	H	Q3b
309	Q1d	H	H	Q3c
310	Q1d	H	H	Q3d
311	Q1d	H	H	Q3e
312	Q1d	H	H	Q3f
313	Q1d	H	H	Q3g

314	Q1d	H	H	Q3h
315	Q1d	H	H	Q3i
316	Q1d	H	H	Q3j
317	Q1d	H	H	Q3k
318	Q1d	H	H	Q3l
319	Q1d	H	H	Q3m
320	Q1d	H	H	Q3n
321	Q1d	H	H	Q3o
322	Q1d	H	H	Q3p
323	Q1d	H	H	Q3q
324	Q1d	H	Me	Q3a
325	Q1d	H	Me	Q3b
326	Q1d	H	Me	Q3c
327	Q1d	H	Me	Q3d
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329	Q1d	H	Me	Q3f
330	Q1d	H	Me	Q3g
331	Q1d	H	Me	Q3h
332	Q1d	H	Me	Q3i
333	Q1d	H	Me	Q3j
334	Q1d	H	Me	Q3k
335	Q1d	H	Me	Q3l
336	Q1d	H	Me	Q3m
337	Q1d	H	Me	Q3n
338	Q1d	H	Me	Q3o
339	Q1d	H	Me	Q3p
340	Q1d	H	Me	Q3q
341	Q1d	Me	H	Q3a
342	Q1d	Me	H	Q3b
343	Q1d	Me	H	Q3c
344	Q1d	Me	H	Q3d
345	Q1d	Me	H	Q3e
346	Q1d	Me	H	Q3f
347	Q1d	Me	H	Q3g
348	Q1d	Me	H	Q3h
349	Q1d	Me	H	Q3i
350	Q1d	Me	H	Q3j
351	Q1d	Me	H	Q3k
352	Q1d	Me	H	Q3l
353	Q1d	Me	H	Q3m
354	Q1d	Me	H	Q3n
355	Q1d	Me	H	Q3o
356	Q1d	Me	H	Q3p
357	Q1d	Me	H	Q3q
358	Q1d	Me	Me	Q3a

359	Q1d	Me	Me	Q3b
360	Q1d	Me	Me	Q3c
361	Q1d	Me	Me	Q3d
362	Q1d	Me	Me	Q3e
363	Q1d	Me	Me	Q3f
364	Q1d	Me	Me	Q3g
365	Q1d	Me	Me	Q3h
366	Q1d	Me	Me	Q3i
367	Q1d	Me	Me	Q3j
368	Q1d	Me	Me	Q3k
369	Q1d	Me	Me	Q3l
370	Q1d	Me	Me	Q3m
371	Q1d	Me	Me	Q3n
372	Q1d	Me	Me	Q3o
373	Q1d	Me	Me	Q3p
374	Q1d	Me	Me	Q3q
375	Q1d	CF3	H	Q3a
376	Q1d	CF3	H	Q3b
377	Q1d	CF3	H	Q3c
378	Q1d	CF3	H	Q3d
379	Q1d	CF3	H	Q3e
380	Q1d	CF3	H	Q3f
381	Q1d	CF3	H	Q3g
382	Q1d	CF3	H	Q3h
383	Q1d	CF3	H	Q3i
384	Q1d	CF3	H	Q3j
385	Q1d	CF3	H	Q3k
386	Q1d	CF3	H	Q3l
387	Q1d	CF3	H	Q3m
388	Q1d	CF3	H	Q3n
389	Q1d	CF3	H	Q3o
390	Q1d	CF3	H	Q3p
391	Q1d	CF3	H	Q3q
392	Q1d	CF3	Me	Q3a
393	Q1d	CF3	Me	Q3b
394	Q1d	CF3	Me	Q3c
395	Q1d	CF3	Me	Q3d
396	Q1d	CF3	Me	Q3e
397	Q1d	CF3	Me	Q3f
398	Q1d	CF3	Me	Q3g
399	Q1d	CF3	Me	Q3h
400	Q1d	CF3	Me	Q3i
401	Q1d	CF3	Me	Q3j
402	Q1d	CF3	Me	Q3k
403	Q1d	CF3	Me	Q3l

404	Q1d	CF3	Me	Q3m
405	Q1d	CF3	Me	Q3n
406	Q1d	CF3	Me	Q3o
407	Q1d	CF3	Me	Q3p
408	Q1d	CF3	Me	Q3q
409	Q1e	H	H	Q3a
410	Q1e	H	H	Q3b
411	Q1e	H	H	Q3c
412	Q1e	H	H	Q3d
413	Q1e	H	H	Q3e
414	Q1e	H	H	Q3f
415	Q1e	H	H	Q3g
416	Q1e	H	H	Q3h
417	Q1e	H	H	Q3i
418	Q1e	H	H	Q3j
419	Q1e	H	H	Q3k
420	Q1e	H	H	Q3l
421	Q1e	H	H	Q3m
422	Q1e	H	H	Q3n
423	Q1e	H	H	Q3o
424	Q1e	H	H	Q3p
425	Q1e	H	H	Q3q
426	Q1e	H	Me	Q3a
427	Q1e	H	Me	Q3b
428	Q1e	H	Me	Q3c
429	Q1e	H	Me	Q3d
430	Q1e	H	Me	Q3e
431	Q1e	H	Me	Q3f
432	Q1e	H	Me	Q3g
433	Q1e	H	Me	Q3h
434	Q1e	H	Me	Q3i
435	Q1e	H	Me	Q3j
436	Q1e	H	Me	Q3k
437	Q1e	H	Me	Q3l
438	Q1e	H	Me	Q3m
439	Q1e	H	Me	Q3n
440	Q1e	H	Me	Q3o
441	Q1e	H	Me	Q3p
442	Q1e	H	Me	Q3q
443	Q1e	Me	H	Q3a
444	Q1e	Me	H	Q3b
445	Q1e	Me	H	Q3c
446	Q1e	Me	H	Q3d
447	Q1e	Me	H	Q3e
448	Q1e	Me	H	Q3f

449	Q1e	Me	H	Q3g
450	Q1e	Me	H	Q3h
451	Q1e	Me	H	Q3i
452	Q1e	Me	H	Q3j
453	Q1e	Me	H	Q3k
454	Q1e	Me	H	Q3l
455	Q1e	Me	H	Q3m
456	Q1e	Me	H	Q3n
457	Q1e	Me	H	Q3o
458	Q1e	Me	H	Q3p
459	Q1e	Me	H	Q3q
460	Q1e	Me	Me	Q3a
461	Q1e	Me	Me	Q3b
462	Q1e	Me	Me	Q3c
463	Q1e	Me	Me	Q3d
464	Q1e	Me	Me	Q3e
465	Q1e	Me	Me	Q3f
466	Q1e	Me	Me	Q3g
467	Q1e	Me	Me	Q3h
468	Q1e	Me	Me	Q3i
469	Q1e	Me	Me	Q3j
470	Q1e	Me	Me	Q3k
471	Q1e	Me	Me	Q3l
472	Q1e	Me	Me	Q3m
473	Q1e	Me	Me	Q3n
474	Q1e	Me	Me	Q3o
475	Q1e	Me	Me	Q3p
476	Q1e	Me	Me	Q3q
477	Q1e	CF3	H	Q3a
478	Q1e	CF3	H	Q3b
479	Q1e	CF3	H	Q3c
480	Q1e	CF3	H	Q3d
481	Q1e	CF3	H	Q3e
482	Q1e	CF3	H	Q3f
483	Q1e	CF3	H	Q3g
484	Q1e	CF3	H	Q3h
485	Q1e	CF3	H	Q3i
486	Q1e	CF3	H	Q3j
487	Q1e	CF3	H	Q3k
488	Q1e	CF3	H	Q3l
489	Q1e	CF3	H	Q3m
490	Q1e	CF3	H	Q3n
491	Q1e	CF3	H	Q3o
492	Q1e	CF3	H	Q3p
493	Q1e	CF3	H	Q3q

494	Q1e	CF3	Me	Q3a
495	Q1e	CF3	Me	Q3b
496	Q1e	CF3	Me	Q3c
497	Q1e	CF3	Me	Q3d
498	Q1e	CF3	Me	Q3e
499	Q1e	CF3	Me	Q3f
500	Q1e	CF3	Me	Q3g
501	Q1e	CF3	Me	Q3h
502	Q1e	CF3	Me	Q3i
503	Q1e	CF3	Me	Q3j
504	Q1e	CF3	Me	Q3k
505	Q1e	CF3	Me	Q3l
506	Q1e	CF3	Me	Q3m
507	Q1e	CF3	Me	Q3n
508	Q1e	CF3	Me	Q3o
509	Q1e	CF3	Me	Q3p
510	Q1e	CF3	Me	Q3q
511	Q1f	H	H	Q3a
512	Q1f	H	H	Q3b
513	Q1f	H	H	Q3c
514	Q1f	H	H	Q3d
515	Q1f	H	H	Q3e
516	Q1f	H	H	Q3f
517	Q1f	H	H	Q3g
518	Q1f	H	H	Q3h
519	Q1f	H	H	Q3i
520	Q1f	H	H	Q3j
521	Q1f	H	H	Q3k
522	Q1f	H	H	Q3l
523	Q1f	H	H	Q3m
524	Q1f	H	H	Q3n
525	Q1f	H	H	Q3o
526	Q1f	H	H	Q3p
527	Q1f	H	H	Q3q
528	Q1f	H	Me	Q3a
529	Q1f	H	Me	Q3b
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531	Q1f	H	Me	Q3d
532	Q1f	H	Me	Q3e
533	Q1f	H	Me	Q3f
534	Q1f	H	Me	Q3g
535	Q1f	H	Me	Q3h
536	Q1f	H	Me	Q3i
537	Q1f	H	Me	Q3j
538	Q1f	H	Me	Q3k

539	Q1f	H	Me	Q3l
540	Q1f	H	Me	Q3m
541	Q1f	H	Me	Q3n
542	Q1f	H	Me	Q3o
543	Q1f	H	Me	Q3p
544	Q1f	H	Me	Q3q
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546	Q1f	Me	H	Q3b
547	Q1f	Me	H	Q3c
548	Q1f	Me	H	Q3d
549	Q1f	Me	H	Q3e
550	Q1f	Me	H	Q3f
551	Q1f	Me	H	Q3g
552	Q1f	Me	H	Q3h
553	Q1f	Me	H	Q3i
554	Q1f	Me	H	Q3j
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557	Q1f	Me	H	Q3m
558	Q1f	Me	H	Q3n
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560	Q1f	Me	H	Q3p
561	Q1f	Me	H	Q3q
562	Q1f	Me	Me	Q3a
563	Q1f	Me	Me	Q3b
564	Q1f	Me	Me	Q3c
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566	Q1f	Me	Me	Q3e
567	Q1f	Me	Me	Q3f
568	Q1f	Me	Me	Q3g
569	Q1f	Me	Me	Q3h
570	Q1f	Me	Me	Q3i
571	Q1f	Me	Me	Q3j
572	Q1f	Me	Me	Q3k
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574	Q1f	Me	Me	Q3m
575	Q1f	Me	Me	Q3n
576	Q1f	Me	Me	Q3o
577	Q1f	Me	Me	Q3p
578	Q1f	Me	Me	Q3q
579	Q1f	CF3	H	Q3a
580	Q1f	CF3	H	Q3b
581	Q1f	CF3	H	Q3c
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583	Q1f	CF3	H	Q3e

584	Q1f	CF3	H	Q3f
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586	Q1f	CF3	H	Q3h
587	Q1f	CF3	H	Q3i
588	Q1f	CF3	H	Q3j
589	Q1f	CF3	H	Q3k
590	Q1f	CF3	H	Q3l
591	Q1f	CF3	H	Q3m
592	Q1f	CF3	H	Q3n
593	Q1f	CF3	H	Q3o
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595	Q1f	CF3	H	Q3q
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597	Q1f	CF3	Me	Q3b
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604	Q1f	CF3	Me	Q3i
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608	Q1f	CF3	Me	Q3m
609	Q1f	CF3	Me	Q3n
610	Q1f	CF3	Me	Q3o
611	Q1f	CF3	Me	Q3p
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613	Q1g	H	H	Q3a
614	Q1g	H	H	Q3b
615	Q1g	H	H	Q3c
616	Q1g	H	H	Q3d
617	Q1g	H	H	Q3e
618	Q1g	H	H	Q3f
619	Q1g	H	H	Q3g
620	Q1g	H	H	Q3h
621	Q1g	H	H	Q3i
622	Q1g	H	H	Q3j
623	Q1g	H	H	Q3k
624	Q1g	H	H	Q3l
625	Q1g	H	H	Q3m
626	Q1g	H	H	Q3n
627	Q1g	H	H	Q3o
628	Q1g	H	H	Q3p

629	Q1g	H	H	Q3q
630	Q1g	H	Me	Q3a
631	Q1g	H	Me	Q3b
632	Q1g	H	Me	Q3c
633	Q1g	H	Me	Q3d
634	Q1g	H	Me	Q3e
635	Q1g	H	Me	Q3f
636	Q1g	H	Me	Q3g
637	Q1g	H	Me	Q3h
638	Q1g	H	Me	Q3i
639	Q1g	H	Me	Q3j
640	Q1g	H	Me	Q3k
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642	Q1g	H	Me	Q3m
643	Q1g	H	Me	Q3n
644	Q1g	H	Me	Q3o
645	Q1g	H	Me	Q3p
646	Q1g	H	Me	Q3q
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648	Q1g	Me	H	Q3b
649	Q1g	Me	H	Q3c
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655	Q1g	Me	H	Q3i
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661	Q1g	Me	H	Q3o
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663	Q1g	Me	H	Q3q
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666	Q1g	Me	Me	Q3c
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671	Q1g	Me	Me	Q3h
672	Q1g	Me	Me	Q3i
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674	Q1g	Me	Me	Q3k
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676	Q1g	Me	Me	Q3m
677	Q1g	Me	Me	Q3n
678	Q1g	Me	Me	Q3o
679	Q1g	Me	Me	Q3p
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681	Q1g	CF3	H	Q3a
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687	Q1g	CF3	H	Q3g
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689	Q1g	CF3	H	Q3i
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693	Q1g	CF3	H	Q3m
694	Q1g	CF3	H	Q3n
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715	Q1h	H	H	Q3a
716	Q1h	H	H	Q3b
717	Q1h	H	H	Q3c
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719	Q1h	H	H	Q3e
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721	Q1h	H	H	Q3g
722	Q1h	H	H	Q3h
723	Q1h	H	H	Q3i
724	Q1h	H	H	Q3j
725	Q1h	H	H	Q3k
726	Q1h	H	H	Q3l
727	Q1h	H	H	Q3m
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729	Q1h	H	H	Q3o
730	Q1h	H	H	Q3p
731	Q1h	H	H	Q3q
732	Q1h	H	Me	Q3a
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734	Q1h	H	Me	Q3c
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736	Q1h	H	Me	Q3e
737	Q1h	H	Me	Q3f
738	Q1h	H	Me	Q3g
739	Q1h	H	Me	Q3h
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742	Q1h	H	Me	Q3k
743	Q1h	H	Me	Q3l
744	Q1h	H	Me	Q3m
745	Q1h	H	Me	Q3n
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747	Q1h	H	Me	Q3p
748	Q1h	H	Me	Q3q
749	Q1h	Me	H	Q3a
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751	Q1h	Me	H	Q3c
752	Q1h	Me	H	Q3d
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757	Q1h	Me	H	Q3i
758	Q1h	Me	H	Q3j
759	Q1h	Me	H	Q3k
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761	Q1h	Me	H	Q3m
762	Q1h	Me	H	Q3n
763	Q1h	Me	H	Q3o

764	Q1h	Me	H	Q3p
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766	Q1h	Me	Me	Q3a
767	Q1h	Me	Me	Q3b
768	Q1h	Me	Me	Q3c
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770	Q1h	Me	Me	Q3e
771	Q1h	Me	Me	Q3f
772	Q1h	Me	Me	Q3g
773	Q1h	Me	Me	Q3h
774	Q1h	Me	Me	Q3i
775	Q1h	Me	Me	Q3j
776	Q1h	Me	Me	Q3k
777	Q1h	Me	Me	Q3l
778	Q1h	Me	Me	Q3m
779	Q1h	Me	Me	Q3n
780	Q1h	Me	Me	Q3o
781	Q1h	Me	Me	Q3p
782	Q1h	Me	Me	Q3q
783	Q1h	CF3	H	Q3a
784	Q1h	CF3	H	Q3b
785	Q1h	CF3	H	Q3c
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787	Q1h	CF3	H	Q3e
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789	Q1h	CF3	H	Q3g
790	Q1h	CF3	H	Q3h
791	Q1h	CF3	H	Q3i
792	Q1h	CF3	H	Q3j
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794	Q1h	CF3	H	Q3l
795	Q1h	CF3	H	Q3m
796	Q1h	CF3	H	Q3n
797	Q1h	CF3	H	Q3o
798	Q1h	CF3	H	Q3p
799	Q1h	CF3	H	Q3q
800	Q1h	CF3	Me	Q3a
801	Q1h	CF3	Me	Q3b
802	Q1h	CF3	Me	Q3c
803	Q1h	CF3	Me	Q3d
804	Q1h	CF3	Me	Q3e
805	Q1h	CF3	Me	Q3f
806	Q1h	CF3	Me	Q3g
807	Q1h	CF3	Me	Q3h
808	Q1h	CF3	Me	Q3i

809	Q1h	CF3	Me	Q3j
810	Q1h	CF3	Me	Q3k
811	Q1h	CF3	Me	Q3l
812	Q1h	CF3	Me	Q3m
813	Q1h	CF3	Me	Q3n
814	Q1h	CF3	Me	Q3o
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816	Q1h	CF3	Me	Q3q
817	Q1i	H	H	Q3a
818	Q1i	H	H	Q3b
819	Q1i	H	H	Q3c
820	Q1i	H	H	Q3d
821	Q1i	H	H	Q3e
822	Q1i	H	H	Q3f
823	Q1i	H	H	Q3g
824	Q1i	H	H	Q3h
825	Q1i	H	H	Q3i
826	Q1i	H	H	Q3j
827	Q1i	H	H	Q3k
828	Q1i	H	H	Q3l
829	Q1i	H	H	Q3m
830	Q1i	H	H	Q3n
831	Q1i	H	H	Q3o
832	Q1i	H	H	Q3p
833	Q1i	H	H	Q3q
834	Q1i	H	Me	Q3a
835	Q1i	H	Me	Q3b
836	Q1i	H	Me	Q3c
837	Q1i	H	Me	Q3d
838	Q1i	H	Me	Q3e
839	Q1i	H	Me	Q3f
840	Q1i	H	Me	Q3g
841	Q1i	H	Me	Q3h
842	Q1i	H	Me	Q3i
843	Q1i	H	Me	Q3j
844	Q1i	H	Me	Q3k
845	Q1i	H	Me	Q3l
846	Q1i	H	Me	Q3m
847	Q1i	H	Me	Q3n
848	Q1i	H	Me	Q3o
849	Q1i	H	Me	Q3p
850	Q1i	H	Me	Q3q
851	Q1i	Me	H	Q3a
852	Q1i	Me	H	Q3b
853	Q1i	Me	H	Q3c

854	Q1i	Me	H	Q3d
855	Q1i	Me	H	Q3e
856	Q1i	Me	H	Q3f
857	Q1i	Me	H	Q3g
858	Q1i	Me	H	Q3h
859	Q1i	Me	H	Q3i
860	Q1i	Me	H	Q3j
861	Q1i	Me	H	Q3k
862	Q1i	Me	H	Q3l
863	Q1i	Me	H	Q3m
864	Q1i	Me	H	Q3n
865	Q1i	Me	H	Q3o
866	Q1i	Me	H	Q3p
867	Q1i	Me	H	Q3q
868	Q1i	Me	Me	Q3a
869	Q1i	Me	Me	Q3b
870	Q1i	Me	Me	Q3c
871	Q1i	Me	Me	Q3d
872	Q1i	Me	Me	Q3e
873	Q1i	Me	Me	Q3f
874	Q1i	Me	Me	Q3g
875	Q1i	Me	Me	Q3h
876	Q1i	Me	Me	Q3i
877	Q1i	Me	Me	Q3j
878	Q1i	Me	Me	Q3k
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880	Q1i	Me	Me	Q3m
881	Q1i	Me	Me	Q3n
882	Q1i	Me	Me	Q3o
883	Q1i	Me	Me	Q3p
884	Q1i	Me	Me	Q3q
885	Q1i	CF3	H	Q3a
886	Q1i	CF3	H	Q3b
887	Q1i	CF3	H	Q3c
888	Q1i	CF3	H	Q3d
889	Q1i	CF3	H	Q3e
890	Q1i	CF3	H	Q3f
891	Q1i	CF3	H	Q3g
892	Q1i	CF3	H	Q3h
893	Q1i	CF3	H	Q3i
894	Q1i	CF3	H	Q3j
895	Q1i	CF3	H	Q3k
896	Q1i	CF3	H	Q3l
897	Q1i	CF3	H	Q3m
898	Q1i	CF3	H	Q3n

899	Q1i	CF3	H	Q3o
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901	Q1i	CF3	H	Q3q
902	Q1i	CF3	Me	Q3a
903	Q1i	CF3	Me	Q3b
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910	Q1i	CF3	Me	Q3i
911	Q1i	CF3	Me	Q3j
912	Q1i	CF3	Me	Q3k
913	Q1i	CF3	Me	Q3l
914	Q1i	CF3	Me	Q3m
915	Q1i	CF3	Me	Q3n
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918	Q1i	CF3	Me	Q3q
919	Q1j	H	H	Q3a
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922	Q1j	H	H	Q3d
923	Q1j	H	H	Q3e
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925	Q1j	H	H	Q3g
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933	Q1j	H	H	Q3o
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935	Q1j	H	H	Q3q
936	Q1j	H	Me	Q3a
937	Q1j	H	Me	Q3b
938	Q1j	H	Me	Q3c
939	Q1j	H	Me	Q3d
940	Q1j	H	Me	Q3e
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942	Q1j	H	Me	Q3g
943	Q1j	H	Me	Q3h

944	Q1j	H	Me	Q3i
945	Q1j	H	Me	Q3j
946	Q1j	H	Me	Q3k
947	Q1j	H	Me	Q3l
948	Q1j	H	Me	Q3m
949	Q1j	H	Me	Q3n
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951	Q1j	H	Me	Q3p
952	Q1j	H	Me	Q3q
953	Q1j	Me	H	Q3a
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955	Q1j	Me	H	Q3c
956	Q1j	Me	H	Q3d
957	Q1j	Me	H	Q3e
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960	Q1j	Me	H	Q3h
961	Q1j	Me	H	Q3i
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963	Q1j	Me	H	Q3k
964	Q1j	Me	H	Q3l
965	Q1j	Me	H	Q3m
966	Q1j	Me	H	Q3n
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971	Q1j	Me	Me	Q3b
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973	Q1j	Me	Me	Q3d
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976	Q1j	Me	Me	Q3g
977	Q1j	Me	Me	Q3h
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979	Q1j	Me	Me	Q3j
980	Q1j	Me	Me	Q3k
981	Q1j	Me	Me	Q3l
982	Q1j	Me	Me	Q3m
983	Q1j	Me	Me	Q3n
984	Q1j	Me	Me	Q3o
985	Q1j	Me	Me	Q3p
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987	Q1j	CF3	H	Q3a
988	Q1j	CF3	H	Q3b

989	Q1j	CF3	H	Q3c
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991	Q1j	CF3	H	Q3e
992	Q1j	CF3	H	Q3f
993	Q1j	CF3	H	Q3g
994	Q1j	CF3	H	Q3h
995	Q1j	CF3	H	Q3i
996	Q1j	CF3	H	Q3j
997	Q1j	CF3	H	Q3k
998	Q1j	CF3	H	Q3l
999	Q1j	CF3	H	Q3m
1000	Q1j	CF3	H	Q3n
1001	Q1j	CF3	H	Q3o
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1003	Q1j	CF3	H	Q3q
1004	Q1j	CF3	Me	Q3a
1005	Q1j	CF3	Me	Q3b
1006	Q1j	CF3	Me	Q3c
1007	Q1j	CF3	Me	Q3d
1008	Q1j	CF3	Me	Q3e
1009	Q1j	CF3	Me	Q3f
1010	Q1j	CF3	Me	Q3g
1011	Q1j	CF3	Me	Q3h
1012	Q1j	CF3	Me	Q3i
1013	Q1j	CF3	Me	Q3j
1014	Q1j	CF3	Me	Q3k
1015	Q1j	CF3	Me	Q3l
1016	Q1j	CF3	Me	Q3m
1017	Q1j	CF3	Me	Q3n
1018	Q1j	CF3	Me	Q3o
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1020	Q1j	CF3	Me	Q3q
1021	Q1k	H	H	Q3a
1022	Q1k	H	H	Q3b
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1024	Q1k	H	H	Q3d
1025	Q1k	H	H	Q3e
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1027	Q1k	H	H	Q3g
1028	Q1k	H	H	Q3h
1029	Q1k	H	H	Q3i
1030	Q1k	H	H	Q3j
1031	Q1k	H	H	Q3k
1032	Q1k	H	H	Q3l
1033	Q1k	H	H	Q3m

1034	Q1k	H	H	Q3n
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1036	Q1k	H	H	Q3p
1037	Q1k	H	H	Q3q
1038	Q1k	H	Me	Q3a
1039	Q1k	H	Me	Q3b
1040	Q1k	H	Me	Q3c
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1044	Q1k	H	Me	Q3g
1045	Q1k	H	Me	Q3h
1046	Q1k	H	Me	Q3i
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1129	Q1l	H	H	Q3g
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1379	Q1n	Me	Me	Q3b
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1497	Q1o	CF3	H	Q3a
1498	Q1o	CF3	H	Q3b
1499	Q1o	CF3	H	Q3c
1500	Q1o	CF3	H	Q3d
1501	Q1o	CF3	H	Q3e
1502	Q1o	CF3	H	Q3f
1503	Q1o	CF3	H	Q3g
1504	Q1o	CF3	H	Q3h
1505	Q1o	CF3	H	Q3i
1506	Q1o	CF3	H	Q3j
1507	Q1o	CF3	H	Q3k
1508	Q1o	CF3	H	Q3l
1509	Q1o	CF3	H	Q3m
1510	Q1o	CF3	H	Q3n
1511	Q1o	CF3	H	Q3o
1512	Q1o	CF3	H	Q3p
1513	Q1o	CF3	H	Q3q
1514	Q1o	CF3	Me	Q3a
1515	Q1o	CF3	Me	Q3b
1516	Q1o	CF3	Me	Q3c
1517	Q1o	CF3	Me	Q3d
1518	Q1o	CF3	Me	Q3e
1519	Q1o	CF3	Me	Q3f
1520	Q1o	CF3	Me	Q3g
1521	Q1o	CF3	Me	Q3h
1522	Q1o	CF3	Me	Q3i
1523	Q1o	CF3	Me	Q3j
1524	Q1o	CF3	Me	Q3k
1525	Q1o	CF3	Me	Q3l
1526	Q1o	CF3	Me	Q3m
1527	Q1o	CF3	Me	Q3n
1528	Q1o	CF3	Me	Q3o

1529	Q1o	CF3	Me	Q3p
1530	Q1o	CF3	Me	Q3q
1531	Q1p	H	H	Q3a
1532	Q1p	H	H	Q3b
1533	Q1p	H	H	Q3c
1534	Q1p	H	H	Q3d
1535	Q1p	H	H	Q3e
1536	Q1p	H	H	Q3f
1537	Q1p	H	H	Q3g
1538	Q1p	H	H	Q3h
1539	Q1p	H	H	Q3i
1540	Q1p	H	H	Q3j
1541	Q1p	H	H	Q3k
1542	Q1p	H	H	Q3l
1543	Q1p	H	H	Q3m
1544	Q1p	H	H	Q3n
1545	Q1p	H	H	Q3o
1546	Q1p	H	H	Q3p
1547	Q1p	H	H	Q3q
1548	Q1p	H	Me	Q3a
1549	Q1p	H	Me	Q3b
1550	Q1p	H	Me	Q3c
1551	Q1p	H	Me	Q3d
1552	Q1p	H	Me	Q3e
1553	Q1p	H	Me	Q3f
1554	Q1p	H	Me	Q3g
1555	Q1p	H	Me	Q3h
1556	Q1p	H	Me	Q3i
1557	Q1p	H	Me	Q3j
1558	Q1p	H	Me	Q3k
1559	Q1p	H	Me	Q3l
1560	Q1p	H	Me	Q3m
1561	Q1p	H	Me	Q3n
1562	Q1p	H	Me	Q3o
1563	Q1p	H	Me	Q3p
1564	Q1p	H	Me	Q3q
1565	Q1p	Me	H	Q3a
1566	Q1p	Me	H	Q3b
1567	Q1p	Me	H	Q3c
1568	Q1p	Me	H	Q3d
1569	Q1p	Me	H	Q3e
1570	Q1p	Me	H	Q3f
1571	Q1p	Me	H	Q3g
1572	Q1p	Me	H	Q3h
1573	Q1p	Me	H	Q3i

1574	Q1p	Me	H	Q3j
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1576	Q1p	Me	H	Q3l
1577	Q1p	Me	H	Q3m
1578	Q1p	Me	H	Q3n
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1581	Q1p	Me	H	Q3q
1582	Q1p	Me	Me	Q3a
1583	Q1p	Me	Me	Q3b
1584	Q1p	Me	Me	Q3c
1585	Q1p	Me	Me	Q3d
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1588	Q1p	Me	Me	Q3g
1589	Q1p	Me	Me	Q3h
1590	Q1p	Me	Me	Q3i
1591	Q1p	Me	Me	Q3j
1592	Q1p	Me	Me	Q3k
1593	Q1p	Me	Me	Q3l
1594	Q1p	Me	Me	Q3m
1595	Q1p	Me	Me	Q3n
1596	Q1p	Me	Me	Q3o
1597	Q1p	Me	Me	Q3p
1598	Q1p	Me	Me	Q3q
1599	Q1p	CF3	H	Q3a
1600	Q1p	CF3	H	Q3b
1601	Q1p	CF3	H	Q3c
1602	Q1p	CF3	H	Q3d
1603	Q1p	CF3	H	Q3e
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1605	Q1p	CF3	H	Q3g
1606	Q1p	CF3	H	Q3h
1607	Q1p	CF3	H	Q3i
1608	Q1p	CF3	H	Q3j
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1610	Q1p	CF3	H	Q3l
1611	Q1p	CF3	H	Q3m
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1614	Q1p	CF3	H	Q3p
1615	Q1p	CF3	H	Q3q
1616	Q1p	CF3	Me	Q3a
1617	Q1p	CF3	Me	Q3b
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1619	Q1p	CF3	Me	Q3d
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1621	Q1p	CF3	Me	Q3f
1622	Q1p	CF3	Me	Q3g
1623	Q1p	CF3	Me	Q3h
1624	Q1p	CF3	Me	Q3i
1625	Q1p	CF3	Me	Q3j
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1627	Q1p	CF3	Me	Q3l
1628	Q1p	CF3	Me	Q3m
1629	Q1p	CF3	Me	Q3n
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1631	Q1p	CF3	Me	Q3p
1632	Q1p	CF3	Me	Q3q
1633	Q1q	H	H	Q3a
1634	Q1q	H	H	Q3b
1635	Q1q	H	H	Q3c
1636	Q1q	H	H	Q3d
1637	Q1q	H	H	Q3e
1638	Q1q	H	H	Q3f
1639	Q1q	H	H	Q3g
1640	Q1q	H	H	Q3h
1641	Q1q	H	H	Q3i
1642	Q1q	H	H	Q3j
1643	Q1q	H	H	Q3k
1644	Q1q	H	H	Q3l
1645	Q1q	H	H	Q3m
1646	Q1q	H	H	Q3n
1647	Q1q	H	H	Q3o
1648	Q1q	H	H	Q3p
1649	Q1q	H	H	Q3q
1650	Q1q	H	Me	Q3a
1651	Q1q	H	Me	Q3b
1652	Q1q	H	Me	Q3c
1653	Q1q	H	Me	Q3d
1654	Q1q	H	Me	Q3e
1655	Q1q	H	Me	Q3f
1656	Q1q	H	Me	Q3g
1657	Q1q	H	Me	Q3h
1658	Q1q	H	Me	Q3i
1659	Q1q	H	Me	Q3j
1660	Q1q	H	Me	Q3k
1661	Q1q	H	Me	Q3l
1662	Q1q	H	Me	Q3m
1663	Q1q	H	Me	Q3n

1664	Q1q	H	Me	Q3o
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1666	Q1q	H	Me	Q3q
1667	Q1q	Me	H	Q3a
1668	Q1q	Me	H	Q3b
1669	Q1q	Me	H	Q3c
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1681	Q1q	Me	H	Q3o
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1683	Q1q	Me	H	Q3q
1684	Q1q	Me	Me	Q3a
1685	Q1q	Me	Me	Q3b
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1691	Q1q	Me	Me	Q3h
1692	Q1q	Me	Me	Q3i
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1697	Q1q	Me	Me	Q3n
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1699	Q1q	Me	Me	Q3p
1700	Q1q	Me	Me	Q3q
1701	Q1q	CF3	H	Q3a
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1707	Q1q	CF3	H	Q3g
1708	Q1q	CF3	H	Q3h

1709	Q1q	CF3	H	Q3i
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1712	Q1q	CF3	H	Q3l
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1724	Q1q	CF3	Me	Q3g
1725	Q1q	CF3	Me	Q3h
1726	Q1q	CF3	Me	Q3i
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1731	Q1q	CF3	Me	Q3n
1732	Q1q	CF3	Me	Q3o
1733	Q1q	CF3	Me	Q3p
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1735	Q1r	H	H	Q3a
1736	Q1r	H	H	Q3b
1737	Q1r	H	H	Q3c
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1740	Q1r	H	H	Q3f
1741	Q1r	H	H	Q3g
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1743	Q1r	H	H	Q3i
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1749	Q1r	H	H	Q3o
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1751	Q1r	H	H	Q3q
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1763	Q1r	H	Me	Q3l
1764	Q1r	H	Me	Q3m
1765	Q1r	H	Me	Q3n
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1785	Q1r	Me	H	Q3q
1786	Q1r	Me	Me	Q3a
1787	Q1r	Me	Me	Q3b
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1799	Q1r	Me	Me	Q3n
1800	Q1r	Me	Me	Q3o
1801	Q1r	Me	Me	Q3p
1802	Q1r	Me	Me	Q3q
1803	Q1r	CF3	H	Q3a
1804	Q1r	CF3	H	Q3b
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1820	Q1r	CF3	Me	Q3a
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1823	Q1r	CF3	Me	Q3d
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1827	Q1r	CF3	Me	Q3h
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1831	Q1r	CF3	Me	Q3l
1832	Q1r	CF3	Me	Q3m
1833	Q1r	CF3	Me	Q3n
1834	Q1r	CF3	Me	Q3o
1835	Q1r	CF3	Me	Q3p
1836	Q1r	CF3	Me	Q3q
1837	Q1s	H	H	Q3a
1838	Q1s	H	H	Q3b
1839	Q1s	H	H	Q3c
1840	Q1s	H	H	Q3d
1841	Q1s	H	H	Q3e
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1844	Q1s	H	H	Q3h
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1846	Q1s	H	H	Q3j
1847	Q1s	H	H	Q3k
1848	Q1s	H	H	Q3l
1849	Q1s	H	H	Q3m
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1851	Q1s	H	H	Q3o
1852	Q1s	H	H	Q3p
1853	Q1s	H	H	Q3q
1854	Q1s	H	Me	Q3a
1855	Q1s	H	Me	Q3b
1856	Q1s	H	Me	Q3c
1857	Q1s	H	Me	Q3d
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1884	Q1s	Me	H	Q3n
1885	Q1s	Me	H	Q3o
1886	Q1s	Me	H	Q3p
1887	Q1s	Me	H	Q3q
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1891	Q1s	Me	Me	Q3d
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1893	Q1s	Me	Me	Q3f
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1900	Q1s	Me	Me	Q3m
1901	Q1s	Me	Me	Q3n
1902	Q1s	Me	Me	Q3o
1903	Q1s	Me	Me	Q3p
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1905	Q1s	CF3	H	Q3a
1906	Q1s	CF3	H	Q3b
1907	Q1s	CF3	H	Q3c
1908	Q1s	CF3	H	Q3d
1909	Q1s	CF3	H	Q3e
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1913	Q1s	CF3	H	Q3i
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1925	Q1s	CF3	Me	Q3d
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1928	Q1s	CF3	Me	Q3g
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1932	Q1s	CF3	Me	Q3k
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1934	Q1s	CF3	Me	Q3m
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1936	Q1s	CF3	Me	Q3o
1937	Q1s	CF3	Me	Q3p
1938	Q1s	CF3	Me	Q3q
1939	Q1t	H	H	Q3a
1940	Q1t	H	H	Q3b
1941	Q1t	H	H	Q3c
1942	Q1t	H	H	Q3d
1943	Q1t	H	H	Q3e
1944	Q1t	H	H	Q3f
1945	Q1t	H	H	Q3g
1946	Q1t	H	H	Q3h
1947	Q1t	H	H	Q3i
1948	Q1t	H	H	Q3j
1949	Q1t	H	H	Q3k
1950	Q1t	H	H	Q3l
1951	Q1t	H	H	Q3m
1952	Q1t	H	H	Q3n
1953	Q1t	H	H	Q3o
1954	Q1t	H	H	Q3p
1955	Q1t	H	H	Q3q
1956	Q1t	H	Me	Q3a
1957	Q1t	H	Me	Q3b
1958	Q1t	H	Me	Q3c
1959	Q1t	H	Me	Q3d
1960	Q1t	H	Me	Q3e
1961	Q1t	H	Me	Q3f
1962	Q1t	H	Me	Q3g
1963	Q1t	H	Me	Q3h
1964	Q1t	H	Me	Q3i
1965	Q1t	H	Me	Q3j
1966	Q1t	H	Me	Q3k
1967	Q1t	H	Me	Q3l
1968	Q1t	H	Me	Q3m
1969	Q1t	H	Me	Q3n
1970	Q1t	H	Me	Q3o
1971	Q1t	H	Me	Q3p
1972	Q1t	H	Me	Q3q
1973	Q1t	Me	H	Q3a
1974	Q1t	Me	H	Q3b
1975	Q1t	Me	H	Q3c
1976	Q1t	Me	H	Q3d
1977	Q1t	Me	H	Q3e
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1979	Q1t	Me	H	Q3g
1980	Q1t	Me	H	Q3h
1981	Q1t	Me	H	Q3i
1982	Q1t	Me	H	Q3j
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1984	Q1t	Me	H	Q3l
1985	Q1t	Me	H	Q3m
1986	Q1t	Me	H	Q3n
1987	Q1t	Me	H	Q3o
1988	Q1t	Me	H	Q3p
1989	Q1t	Me	H	Q3q
1990	Q1t	Me	Me	Q3a
1991	Q1t	Me	Me	Q3b
1992	Q1t	Me	Me	Q3c
1993	Q1t	Me	Me	Q3d
1994	Q1t	Me	Me	Q3e
1995	Q1t	Me	Me	Q3f
1996	Q1t	Me	Me	Q3g
1997	Q1t	Me	Me	Q3h
1998	Q1t	Me	Me	Q3i
1999	Q1t	Me	Me	Q3j
2000	Q1t	Me	Me	Q3k
2001	Q1t	Me	Me	Q3l
2002	Q1t	Me	Me	Q3m
2003	Q1t	Me	Me	Q3n
2004	Q1t	Me	Me	Q3o
2005	Q1t	Me	Me	Q3p
2006	Q1t	Me	Me	Q3q
2007	Q1t	CF3	H	Q3a
2008	Q1t	CF3	H	Q3b
2009	Q1t	CF3	H	Q3c
2010	Q1t	CF3	H	Q3d
2011	Q1t	CF3	H	Q3e
2012	Q1t	CF3	H	Q3f
2013	Q1t	CF3	H	Q3g
2014	Q1t	CF3	H	Q3h
2015	Q1t	CF3	H	Q3i
2016	Q1t	CF3	H	Q3j
2017	Q1t	CF3	H	Q3k
2018	Q1t	CF3	H	Q3l
2019	Q1t	CF3	H	Q3m
2020	Q1t	CF3	H	Q3n
2021	Q1t	CF3	H	Q3o
2022	Q1t	CF3	H	Q3p
2023	Q1t	CF3	H	Q3q

2024	Q1t	CF3	Me	Q3a
2025	Q1t	CF3	Me	Q3b
2026	Q1t	CF3	Me	Q3c
2027	Q1t	CF3	Me	Q3d
2028	Q1t	CF3	Me	Q3e
2029	Q1t	CF3	Me	Q3f
2030	Q1t	CF3	Me	Q3g
2031	Q1t	CF3	Me	Q3h
2032	Q1t	CF3	Me	Q3i
2033	Q1t	CF3	Me	Q3j
2034	Q1t	CF3	Me	Q3k
2035	Q1t	CF3	Me	Q3l
2036	Q1t	CF3	Me	Q3m
2037	Q1t	CF3	Me	Q3n
2038	Q1t	CF3	Me	Q3o
2039	Q1t	CF3	Me	Q3p
2040	Q1t	CF3	Me	Q3q
2041	Q1u	H	H	Q3a
2042	Q1u	H	H	Q3b
2043	Q1u	H	H	Q3c
2044	Q1u	H	H	Q3d
2045	Q1u	H	H	Q3e
2046	Q1u	H	H	Q3f
2047	Q1u	H	H	Q3g
2048	Q1u	H	H	Q3h
2049	Q1u	H	H	Q3i
2050	Q1u	H	H	Q3j
2051	Q1u	H	H	Q3k
2052	Q1u	H	H	Q3l
2053	Q1u	H	H	Q3m
2054	Q1u	H	H	Q3n
2055	Q1u	H	H	Q3o
2056	Q1u	H	H	Q3p
2057	Q1u	H	H	Q3q
2058	Q1u	H	Me	Q3a
2059	Q1u	H	Me	Q3b
2060	Q1u	H	Me	Q3c
2061	Q1u	H	Me	Q3d
2062	Q1u	H	Me	Q3e
2063	Q1u	H	Me	Q3f
2064	Q1u	H	Me	Q3g
2065	Q1u	H	Me	Q3h
2066	Q1u	H	Me	Q3i
2067	Q1u	H	Me	Q3j
2068	Q1u	H	Me	Q3k

2069	Q1u	H	Me	Q3l
2070	Q1u	H	Me	Q3m
2071	Q1u	H	Me	Q3n
2072	Q1u	H	Me	Q3o
2073	Q1u	H	Me	Q3p
2074	Q1u	H	Me	Q3q
2075	Q1u	Me	H	Q3a
2076	Q1u	Me	H	Q3b
2077	Q1u	Me	H	Q3c
2078	Q1u	Me	H	Q3d
2079	Q1u	Me	H	Q3e
2080	Q1u	Me	H	Q3f
2081	Q1u	Me	H	Q3g
2082	Q1u	Me	H	Q3h
2083	Q1u	Me	H	Q3i
2084	Q1u	Me	H	Q3j
2085	Q1u	Me	H	Q3k
2086	Q1u	Me	H	Q3l
2087	Q1u	Me	H	Q3m
2088	Q1u	Me	H	Q3n
2089	Q1u	Me	H	Q3o
2090	Q1u	Me	H	Q3p
2091	Q1u	Me	H	Q3q
2092	Q1u	Me	Me	Q3a
2093	Q1u	Me	Me	Q3b
2094	Q1u	Me	Me	Q3c
2095	Q1u	Me	Me	Q3d
2096	Q1u	Me	Me	Q3e
2097	Q1u	Me	Me	Q3f
2098	Q1u	Me	Me	Q3g
2099	Q1u	Me	Me	Q3h
2100	Q1u	Me	Me	Q3i
2101	Q1u	Me	Me	Q3j
2102	Q1u	Me	Me	Q3k
2103	Q1u	Me	Me	Q3l
2104	Q1u	Me	Me	Q3m
2105	Q1u	Me	Me	Q3n
2106	Q1u	Me	Me	Q3o
2107	Q1u	Me	Me	Q3p
2108	Q1u	Me	Me	Q3q
2109	Q1u	CF3	H	Q3a
2110	Q1u	CF3	H	Q3b
2111	Q1u	CF3	H	Q3c
2112	Q1u	CF3	H	Q3d
2113	Q1u	CF3	H	Q3e

2114	Q1u	CF3	H	Q3f
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2116	Q1u	CF3	H	Q3h
2117	Q1u	CF3	H	Q3i
2118	Q1u	CF3	H	Q3j
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2121	Q1u	CF3	H	Q3m
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2123	Q1u	CF3	H	Q3o
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2125	Q1u	CF3	H	Q3q
2126	Q1u	CF3	Me	Q3a
2127	Q1u	CF3	Me	Q3b
2128	Q1u	CF3	Me	Q3c
2129	Q1u	CF3	Me	Q3d
2130	Q1u	CF3	Me	Q3e
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2132	Q1u	CF3	Me	Q3g
2133	Q1u	CF3	Me	Q3h
2134	Q1u	CF3	Me	Q3i
2135	Q1u	CF3	Me	Q3j
2136	Q1u	CF3	Me	Q3k
2137	Q1u	CF3	Me	Q3l
2138	Q1u	CF3	Me	Q3m
2139	Q1u	CF3	Me	Q3n
2140	Q1u	CF3	Me	Q3o
2141	Q1u	CF3	Me	Q3p
2142	Q1u	CF3	Me	Q3q
2143	Q1v	H	H	Q3a
2144	Q1v	H	H	Q3b
2145	Q1v	H	H	Q3c
2146	Q1v	H	H	Q3d
2147	Q1v	H	H	Q3e
2148	Q1v	H	H	Q3f
2149	Q1v	H	H	Q3g
2150	Q1v	H	H	Q3h
2151	Q1v	H	H	Q3i
2152	Q1v	H	H	Q3j
2153	Q1v	H	H	Q3k
2154	Q1v	H	H	Q3l
2155	Q1v	H	H	Q3m
2156	Q1v	H	H	Q3n
2157	Q1v	H	H	Q3o
2158	Q1v	H	H	Q3p

2159	Q1v	H	H	Q3q
2160	Q1v	H	Me	Q3a
2161	Q1v	H	Me	Q3b
2162	Q1v	H	Me	Q3c
2163	Q1v	H	Me	Q3d
2164	Q1v	H	Me	Q3e
2165	Q1v	H	Me	Q3f
2166	Q1v	H	Me	Q3g
2167	Q1v	H	Me	Q3h
2168	Q1v	H	Me	Q3i
2169	Q1v	H	Me	Q3j
2170	Q1v	H	Me	Q3k
2171	Q1v	H	Me	Q3l
2172	Q1v	H	Me	Q3m
2173	Q1v	H	Me	Q3n
2174	Q1v	H	Me	Q3o
2175	Q1v	H	Me	Q3p
2176	Q1v	H	Me	Q3q
2177	Q1v	Me	H	Q3a
2178	Q1v	Me	H	Q3b
2179	Q1v	Me	H	Q3c
2180	Q1v	Me	H	Q3d
2181	Q1v	Me	H	Q3e
2182	Q1v	Me	H	Q3f
2183	Q1v	Me	H	Q3g
2184	Q1v	Me	H	Q3h
2185	Q1v	Me	H	Q3i
2186	Q1v	Me	H	Q3j
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2189	Q1v	Me	H	Q3m
2190	Q1v	Me	H	Q3n
2191	Q1v	Me	H	Q3o
2192	Q1v	Me	H	Q3p
2193	Q1v	Me	H	Q3q
2194	Q1v	Me	Me	Q3a
2195	Q1v	Me	Me	Q3b
2196	Q1v	Me	Me	Q3c
2197	Q1v	Me	Me	Q3d
2198	Q1v	Me	Me	Q3e
2199	Q1v	Me	Me	Q3f
2200	Q1v	Me	Me	Q3g
2201	Q1v	Me	Me	Q3h
2202	Q1v	Me	Me	Q3i
2203	Q1v	Me	Me	Q3j

2204	Q1v	Me	Me	Q3k
2205	Q1v	Me	Me	Q3l
2206	Q1v	Me	Me	Q3m
2207	Q1v	Me	Me	Q3n
2208	Q1v	Me	Me	Q3o
2209	Q1v	Me	Me	Q3p
2210	Q1v	Me	Me	Q3q
2211	Q1v	CF3	H	Q3a
2212	Q1v	CF3	H	Q3b
2213	Q1v	CF3	H	Q3c
2214	Q1v	CF3	H	Q3d
2215	Q1v	CF3	H	Q3e
2216	Q1v	CF3	H	Q3f
2217	Q1v	CF3	H	Q3g
2218	Q1v	CF3	H	Q3h
2219	Q1v	CF3	H	Q3i
2220	Q1v	CF3	H	Q3j
2221	Q1v	CF3	H	Q3k
2222	Q1v	CF3	H	Q3l
2223	Q1v	CF3	H	Q3m
2224	Q1v	CF3	H	Q3n
2225	Q1v	CF3	H	Q3o
2226	Q1v	CF3	H	Q3p
2227	Q1v	CF3	H	Q3q
2228	Q1v	CF3	Me	Q3a
2229	Q1v	CF3	Me	Q3b
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2234	Q1v	CF3	Me	Q3g
2235	Q1v	CF3	Me	Q3h
2236	Q1v	CF3	Me	Q3i
2237	Q1v	CF3	Me	Q3j
2238	Q1v	CF3	Me	Q3k
2239	Q1v	CF3	Me	Q3l
2240	Q1v	CF3	Me	Q3m
2241	Q1v	CF3	Me	Q3n
2242	Q1v	CF3	Me	Q3o
2243	Q1v	CF3	Me	Q3p
2244	Q1v	CF3	Me	Q3q
2245	Q1w	H	H	Q3a
2246	Q1w	H	H	Q3b
2247	Q1w	H	H	Q3c
2248	Q1w	H	H	Q3d

2249	Q1w	H	H	Q3e
2250	Q1w	H	H	Q3f
2251	Q1w	H	H	Q3g
2252	Q1w	H	H	Q3h
2253	Q1w	H	H	Q3i
2254	Q1w	H	H	Q3j
2255	Q1w	H	H	Q3k
2256	Q1w	H	H	Q3l
2257	Q1w	H	H	Q3m
2258	Q1w	H	H	Q3n
2259	Q1w	H	H	Q3o
2260	Q1w	H	H	Q3p
2261	Q1w	H	H	Q3q
2262	Q1w	H	Me	Q3a
2263	Q1w	H	Me	Q3b
2264	Q1w	H	Me	Q3c
2265	Q1w	H	Me	Q3d
2266	Q1w	H	Me	Q3e
2267	Q1w	H	Me	Q3f
2268	Q1w	H	Me	Q3g
2269	Q1w	H	Me	Q3h
2270	Q1w	H	Me	Q3i
2271	Q1w	H	Me	Q3j
2272	Q1w	H	Me	Q3k
2273	Q1w	H	Me	Q3l
2274	Q1w	H	Me	Q3m
2275	Q1w	H	Me	Q3n
2276	Q1w	H	Me	Q3o
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2278	Q1w	H	Me	Q3q
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2280	Q1w	Me	H	Q3b
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2282	Q1w	Me	H	Q3d
2283	Q1w	Me	H	Q3e
2284	Q1w	Me	H	Q3f
2285	Q1w	Me	H	Q3g
2286	Q1w	Me	H	Q3h
2287	Q1w	Me	H	Q3i
2288	Q1w	Me	H	Q3j
2289	Q1w	Me	H	Q3k
2290	Q1w	Me	H	Q3l
2291	Q1w	Me	H	Q3m
2292	Q1w	Me	H	Q3n
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2294	Q1w	Me	H	Q3p
2295	Q1w	Me	H	Q3q
2296	Q1w	Me	Me	Q3a
2297	Q1w	Me	Me	Q3b
2298	Q1w	Me	Me	Q3c
2299	Q1w	Me	Me	Q3d
2300	Q1w	Me	Me	Q3e
2301	Q1w	Me	Me	Q3f
2302	Q1w	Me	Me	Q3g
2303	Q1w	Me	Me	Q3h
2304	Q1w	Me	Me	Q3i
2305	Q1w	Me	Me	Q3j
2306	Q1w	Me	Me	Q3k
2307	Q1w	Me	Me	Q3l
2308	Q1w	Me	Me	Q3m
2309	Q1w	Me	Me	Q3n
2310	Q1w	Me	Me	Q3o
2311	Q1w	Me	Me	Q3p
2312	Q1w	Me	Me	Q3q
2313	Q1w	CF3	H	Q3a
2314	Q1w	CF3	H	Q3b
2315	Q1w	CF3	H	Q3c
2316	Q1w	CF3	H	Q3d
2317	Q1w	CF3	H	Q3e
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2319	Q1w	CF3	H	Q3g
2320	Q1w	CF3	H	Q3h
2321	Q1w	CF3	H	Q3i
2322	Q1w	CF3	H	Q3j
2323	Q1w	CF3	H	Q3k
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2325	Q1w	CF3	H	Q3m
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2327	Q1w	CF3	H	Q3o
2328	Q1w	CF3	H	Q3p
2329	Q1w	CF3	H	Q3q
2330	Q1w	CF3	Me	Q3a
2331	Q1w	CF3	Me	Q3b
2332	Q1w	CF3	Me	Q3c
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2335	Q1w	CF3	Me	Q3f
2336	Q1w	CF3	Me	Q3g
2337	Q1w	CF3	Me	Q3h
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2339	Q1w	CF3	Me	Q3j
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2341	Q1w	CF3	Me	Q3l
2342	Q1w	CF3	Me	Q3m
2343	Q1w	CF3	Me	Q3n
2344	Q1w	CF3	Me	Q3o
2345	Q1w	CF3	Me	Q3p
2346	Q1w	CF3	Me	Q3q
2347	Q1x	H	H	Q3a
2348	Q1x	H	H	Q3b
2349	Q1x	H	H	Q3c
2350	Q1x	H	H	Q3d
2351	Q1x	H	H	Q3e
2352	Q1x	H	H	Q3f
2353	Q1x	H	H	Q3g
2354	Q1x	H	H	Q3h
2355	Q1x	H	H	Q3i
2356	Q1x	H	H	Q3j
2357	Q1x	H	H	Q3k
2358	Q1x	H	H	Q3l
2359	Q1x	H	H	Q3m
2360	Q1x	H	H	Q3n
2361	Q1x	H	H	Q3o
2362	Q1x	H	H	Q3p
2363	Q1x	H	H	Q3q
2364	Q1x	H	Me	Q3a
2365	Q1x	H	Me	Q3b
2366	Q1x	H	Me	Q3c
2367	Q1x	H	Me	Q3d
2368	Q1x	H	Me	Q3e
2369	Q1x	H	Me	Q3f
2370	Q1x	H	Me	Q3g
2371	Q1x	H	Me	Q3h
2372	Q1x	H	Me	Q3i
2373	Q1x	H	Me	Q3j
2374	Q1x	H	Me	Q3k
2375	Q1x	H	Me	Q3l
2376	Q1x	H	Me	Q3m
2377	Q1x	H	Me	Q3n
2378	Q1x	H	Me	Q3o
2379	Q1x	H	Me	Q3p
2380	Q1x	H	Me	Q3q
2381	Q1x	Me	H	Q3a
2382	Q1x	Me	H	Q3b
2383	Q1x	Me	H	Q3c

2384	Q1x	Me	H	Q3d
2385	Q1x	Me	H	Q3e
2386	Q1x	Me	H	Q3f
2387	Q1x	Me	H	Q3g
2388	Q1x	Me	H	Q3h
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2390	Q1x	Me	H	Q3j
2391	Q1x	Me	H	Q3k
2392	Q1x	Me	H	Q3l
2393	Q1x	Me	H	Q3m
2394	Q1x	Me	H	Q3n
2395	Q1x	Me	H	Q3o
2396	Q1x	Me	H	Q3p
2397	Q1x	Me	H	Q3q
2398	Q1x	Me	Me	Q3a
2399	Q1x	Me	Me	Q3b
2400	Q1x	Me	Me	Q3c
2401	Q1x	Me	Me	Q3d
2402	Q1x	Me	Me	Q3e
2403	Q1x	Me	Me	Q3f
2404	Q1x	Me	Me	Q3g
2405	Q1x	Me	Me	Q3h
2406	Q1x	Me	Me	Q3i
2407	Q1x	Me	Me	Q3j
2408	Q1x	Me	Me	Q3k
2409	Q1x	Me	Me	Q3l
2410	Q1x	Me	Me	Q3m
2411	Q1x	Me	Me	Q3n
2412	Q1x	Me	Me	Q3o
2413	Q1x	Me	Me	Q3p
2414	Q1x	Me	Me	Q3q
2415	Q1x	CF3	H	Q3a
2416	Q1x	CF3	H	Q3b
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2418	Q1x	CF3	H	Q3d
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2421	Q1x	CF3	H	Q3g
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2427	Q1x	CF3	H	Q3m
2428	Q1x	CF3	H	Q3n

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2431	Q1x	CF3	H	Q3q
2432	Q1x	CF3	Me	Q3a
2433	Q1x	CF3	Me	Q3b
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2437	Q1x	CF3	Me	Q3f
2438	Q1x	CF3	Me	Q3g
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2440	Q1x	CF3	Me	Q3i
2441	Q1x	CF3	Me	Q3j
2442	Q1x	CF3	Me	Q3k
2443	Q1x	CF3	Me	Q3l
2444	Q1x	CF3	Me	Q3m
2445	Q1x	CF3	Me	Q3n
2446	Q1x	CF3	Me	Q3o
2447	Q1x	CF3	Me	Q3p
2448	Q1x	CF3	Me	Q3q
2449	Q1y	H	H	Q3a
2450	Q1y	H	H	Q3b
2451	Q1y	H	H	Q3c
2452	Q1y	H	H	Q3d
2453	Q1y	H	H	Q3e
2454	Q1y	H	H	Q3f
2455	Q1y	H	H	Q3g
2456	Q1y	H	H	Q3h
2457	Q1y	H	H	Q3i
2458	Q1y	H	H	Q3j
2459	Q1y	H	H	Q3k
2460	Q1y	H	H	Q3l
2461	Q1y	H	H	Q3m
2462	Q1y	H	H	Q3n
2463	Q1y	H	H	Q3o
2464	Q1y	H	H	Q3p
2465	Q1y	H	H	Q3q
2466	Q1y	H	Me	Q3a
2467	Q1y	H	Me	Q3b
2468	Q1y	H	Me	Q3c
2469	Q1y	H	Me	Q3d
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2471	Q1y	H	Me	Q3f
2472	Q1y	H	Me	Q3g
2473	Q1y	H	Me	Q3h

2474	Q1y	H	Me	Q3i
2475	Q1y	H	Me	Q3j
2476	Q1y	H	Me	Q3k
2477	Q1y	H	Me	Q3l
2478	Q1y	H	Me	Q3m
2479	Q1y	H	Me	Q3n
2480	Q1y	H	Me	Q3o
2481	Q1y	H	Me	Q3p
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2483	Q1y	Me	H	Q3a
2484	Q1y	Me	H	Q3b
2485	Q1y	Me	H	Q3c
2486	Q1y	Me	H	Q3d
2487	Q1y	Me	H	Q3e
2488	Q1y	Me	H	Q3f
2489	Q1y	Me	H	Q3g
2490	Q1y	Me	H	Q3h
2491	Q1y	Me	H	Q3i
2492	Q1y	Me	H	Q3j
2493	Q1y	Me	H	Q3k
2494	Q1y	Me	H	Q3l
2495	Q1y	Me	H	Q3m
2496	Q1y	Me	H	Q3n
2497	Q1y	Me	H	Q3o
2498	Q1y	Me	H	Q3p
2499	Q1y	Me	H	Q3q
2500	Q1y	Me	Me	Q3a
2501	Q1y	Me	Me	Q3b
2502	Q1y	Me	Me	Q3c
2503	Q1y	Me	Me	Q3d
2504	Q1y	Me	Me	Q3e
2505	Q1y	Me	Me	Q3f
2506	Q1y	Me	Me	Q3g
2507	Q1y	Me	Me	Q3h
2508	Q1y	Me	Me	Q3i
2509	Q1y	Me	Me	Q3j
2510	Q1y	Me	Me	Q3k
2511	Q1y	Me	Me	Q3l
2512	Q1y	Me	Me	Q3m
2513	Q1y	Me	Me	Q3n
2514	Q1y	Me	Me	Q3o
2515	Q1y	Me	Me	Q3p
2516	Q1y	Me	Me	Q3q
2517	Q1y	CF3	H	Q3a
2518	Q1y	CF3	H	Q3b

2519	Q1y	CF3	H	Q3c
2520	Q1y	CF3	H	Q3d
2521	Q1y	CF3	H	Q3e
2522	Q1y	CF3	H	Q3f
2523	Q1y	CF3	H	Q3g
2524	Q1y	CF3	H	Q3h
2525	Q1y	CF3	H	Q3i
2526	Q1y	CF3	H	Q3j
2527	Q1y	CF3	H	Q3k
2528	Q1y	CF3	H	Q3l
2529	Q1y	CF3	H	Q3m
2530	Q1y	CF3	H	Q3n
2531	Q1y	CF3	H	Q3o
2532	Q1y	CF3	H	Q3p
2533	Q1y	CF3	H	Q3q
2534	Q1y	CF3	Me	Q3a
2535	Q1y	CF3	Me	Q3b
2536	Q1y	CF3	Me	Q3c
2537	Q1y	CF3	Me	Q3d
2538	Q1y	CF3	Me	Q3e
2539	Q1y	CF3	Me	Q3f
2540	Q1y	CF3	Me	Q3g
2541	Q1y	CF3	Me	Q3h
2542	Q1y	CF3	Me	Q3i
2543	Q1y	CF3	Me	Q3j
2544	Q1y	CF3	Me	Q3k
2545	Q1y	CF3	Me	Q3l
2546	Q1y	CF3	Me	Q3m
2547	Q1y	CF3	Me	Q3n
2548	Q1y	CF3	Me	Q3o
2549	Q1y	CF3	Me	Q3p
2550	Q1y	CF3	Me	Q3q
2551	Q1z	H	H	Q3a
2552	Q1z	H	H	Q3b
2553	Q1z	H	H	Q3c
2554	Q1z	H	H	Q3d
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2556	Q1z	H	H	Q3f
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2561	Q1z	H	H	Q3k
2562	Q1z	H	H	Q3l
2563	Q1z	H	H	Q3m

2564	Q1z	H	H	Q3n
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2566	Q1z	H	H	Q3p
2567	Q1z	H	H	Q3q
2568	Q1z	H	Me	Q3a
2569	Q1z	H	Me	Q3b
2570	Q1z	H	Me	Q3c
2571	Q1z	H	Me	Q3d
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2574	Q1z	H	Me	Q3g
2575	Q1z	H	Me	Q3h
2576	Q1z	H	Me	Q3i
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2604	Q1z	Me	Me	Q3c
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2607	Q1z	Me	Me	Q3f
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2619	Q1z	CF3	H	Q3a
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2651	Q1z	CF3	Me	Q3p
2652	Q1z	CF3	Me	Q3q
2653	Q1a	H	H	Q3r

2654	Q1a	H	H	Q3s
2655	Q1a	H	H	Q3t
2656	Q1a	H	H	Q3u
2657	Q1a	H	Me	Q3r
2658	Q1a	H	Me	Q3s
2659	Q1a	H	Me	Q3t
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2661	Q1a	Me	H	Q3r
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2663	Q1a	Me	H	Q3t
2664	Q1a	Me	H	Q3u
2665	Q1a	Me	Me	Q3r
2666	Q1a	Me	Me	Q3s
2667	Q1a	Me	Me	Q3t
2668	Q1a	Me	Me	Q3u
2669	Q1a	CF3	H	Q3r
2670	Q1a	CF3	H	Q3s
2671	Q1a	CF3	H	Q3t
2672	Q1a	CF3	H	Q3u
2673	Q1a	CF3	Me	Q3r
2674	Q1a	CF3	Me	Q3s
2675	Q1a	CF3	Me	Q3t
2676	Q1a	CF3	Me	Q3u
2677	Q1b	H	H	Q3r
2678	Q1b	H	H	Q3s
2679	Q1b	H	H	Q3t
2680	Q1b	H	H	Q3u
2681	Q1b	H	Me	Q3r
2682	Q1b	H	Me	Q3s
2683	Q1b	H	Me	Q3t
2684	Q1b	H	Me	Q3u
2685	Q1b	Me	H	Q3r
2686	Q1b	Me	H	Q3s
2687	Q1b	Me	H	Q3t
2688	Q1b	Me	H	Q3u
2689	Q1b	Me	Me	Q3r
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2691	Q1b	Me	Me	Q3t
2692	Q1b	Me	Me	Q3u
2693	Q1b	CF3	H	Q3r
2694	Q1b	CF3	H	Q3s
2695	Q1b	CF3	H	Q3t
2696	Q1b	CF3	H	Q3u
2697	Q1b	CF3	Me	Q3r
2698	Q1b	CF3	Me	Q3s

2699	Q1b	CF3	Me	Q3t
2700	Q1b	CF3	Me	Q3u
2701	Q1c	H	H	Q3r
2702	Q1c	H	H	Q3s
2703	Q1c	H	H	Q3t
2704	Q1c	H	H	Q3u
2705	Q1c	H	Me	Q3r
2706	Q1c	H	Me	Q3s
2707	Q1c	H	Me	Q3t
2708	Q1c	H	Me	Q3u
2709	Q1c	Me	H	Q3r
2710	Q1c	Me	H	Q3s
2711	Q1c	Me	H	Q3t
2712	Q1c	Me	H	Q3u
2713	Q1c	Me	Me	Q3r
2714	Q1c	Me	Me	Q3s
2715	Q1c	Me	Me	Q3t
2716	Q1c	Me	Me	Q3u
2717	Q1c	CF3	H	Q3r
2718	Q1c	CF3	H	Q3s
2719	Q1c	CF3	H	Q3t
2720	Q1c	CF3	H	Q3u
2721	Q1c	CF3	Me	Q3r
2722	Q1c	CF3	Me	Q3s
2723	Q1c	CF3	Me	Q3t
2724	Q1c	CF3	Me	Q3u
2725	Q1d	H	H	Q3r
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2729	Q1d	H	Me	Q3r
2730	Q1d	H	Me	Q3s
2731	Q1d	H	Me	Q3t
2732	Q1d	H	Me	Q3u
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2734	Q1d	Me	H	Q3s
2735	Q1d	Me	H	Q3t
2736	Q1d	Me	H	Q3u
2737	Q1d	Me	Me	Q3r
2738	Q1d	Me	Me	Q3s
2739	Q1d	Me	Me	Q3t
2740	Q1d	Me	Me	Q3u
2741	Q1d	CF3	H	Q3r
2742	Q1d	CF3	H	Q3s
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2744	Q1d	CF3	H	Q3u
2745	Q1d	CF3	Me	Q3r
2746	Q1d	CF3	Me	Q3s
2747	Q1d	CF3	Me	Q3t
2748	Q1d	CF3	Me	Q3u
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2753	Q1e	H	Me	Q3r
2754	Q1e	H	Me	Q3s
2755	Q1e	H	Me	Q3t
2756	Q1e	H	Me	Q3u
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2758	Q1e	Me	H	Q3s
2759	Q1e	Me	H	Q3t
2760	Q1e	Me	H	Q3u
2761	Q1e	Me	Me	Q3r
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2763	Q1e	Me	Me	Q3t
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2766	Q1e	CF3	H	Q3s
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2770	Q1e	CF3	Me	Q3s
2771	Q1e	CF3	Me	Q3t
2772	Q1e	CF3	Me	Q3u
2773	Q1f	H	H	Q3r
2774	Q1f	H	H	Q3s
2775	Q1f	H	H	Q3t
2776	Q1f	H	H	Q3u
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2783	Q1f	Me	H	Q3t
2784	Q1f	Me	H	Q3u
2785	Q1f	Me	Me	Q3r
2786	Q1f	Me	Me	Q3s
2787	Q1f	Me	Me	Q3t
2788	Q1f	Me	Me	Q3u

2789	Q1f	CF3	H	Q3r
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2791	Q1f	CF3	H	Q3t
2792	Q1f	CF3	H	Q3u
2793	Q1f	CF3	Me	Q3r
2794	Q1f	CF3	Me	Q3s
2795	Q1f	CF3	Me	Q3t
2796	Q1f	CF3	Me	Q3u
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2798	Q1g	H	H	Q3s
2799	Q1g	H	H	Q3t
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2802	Q1g	H	Me	Q3s
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2807	Q1g	Me	H	Q3t
2808	Q1g	Me	H	Q3u
2809	Q1g	Me	Me	Q3r
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2816	Q1g	CF3	H	Q3u
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2820	Q1g	CF3	Me	Q3u
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2824	Q1h	H	H	Q3u
2825	Q1h	H	Me	Q3r
2826	Q1h	H	Me	Q3s
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2828	Q1h	H	Me	Q3u
2829	Q1h	Me	H	Q3r
2830	Q1h	Me	H	Q3s
2831	Q1h	Me	H	Q3t
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2837	Q1h	CF3	H	Q3r
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2843	Q1h	CF3	Me	Q3t
2844	Q1h	CF3	Me	Q3u
2845	Q1i	H	H	Q3r
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2849	Q1i	H	Me	Q3r
2850	Q1i	H	Me	Q3s
2851	Q1i	H	Me	Q3t
2852	Q1i	H	Me	Q3u
2853	Q1i	Me	H	Q3r
2854	Q1i	Me	H	Q3s
2855	Q1i	Me	H	Q3t
2856	Q1i	Me	H	Q3u
2857	Q1i	Me	Me	Q3r
2858	Q1i	Me	Me	Q3s
2859	Q1i	Me	Me	Q3t
2860	Q1i	Me	Me	Q3u
2861	Q1i	CF3	H	Q3r
2862	Q1i	CF3	H	Q3s
2863	Q1i	CF3	H	Q3t
2864	Q1i	CF3	H	Q3u
2865	Q1i	CF3	Me	Q3r
2866	Q1i	CF3	Me	Q3s
2867	Q1i	CF3	Me	Q3t
2868	Q1i	CF3	Me	Q3u
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2870	Q1j	H	H	Q3s
2871	Q1j	H	H	Q3t
2872	Q1j	H	H	Q3u
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2874	Q1j	H	Me	Q3s
2875	Q1j	H	Me	Q3t
2876	Q1j	H	Me	Q3u
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2882	Q1j	Me	Me	Q3s
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2886	Q1j	CF3	H	Q3s
2887	Q1j	CF3	H	Q3t
2888	Q1j	CF3	H	Q3u
2889	Q1j	CF3	Me	Q3r
2890	Q1j	CF3	Me	Q3s
2891	Q1j	CF3	Me	Q3t
2892	Q1j	CF3	Me	Q3u
2893	Q1k	H	H	Q3r
2894	Q1k	H	H	Q3s
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2897	Q1k	H	Me	Q3r
2898	Q1k	H	Me	Q3s
2899	Q1k	H	Me	Q3t
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2903	Q1k	Me	H	Q3t
2904	Q1k	Me	H	Q3u
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2914	Q1k	CF3	Me	Q3s
2915	Q1k	CF3	Me	Q3t
2916	Q1k	CF3	Me	Q3u
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2921	Q1l	H	Me	Q3r
2922	Q1l	H	Me	Q3s
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2931	Q1l	Me	Me	Q3t
2932	Q1l	Me	Me	Q3u
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2934	Q1l	CF3	H	Q3s
2935	Q1l	CF3	H	Q3t
2936	Q1l	CF3	H	Q3u
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2939	Q1l	CF3	Me	Q3t
2940	Q1l	CF3	Me	Q3u
2941	Q1m	H	H	Q3r
2942	Q1m	H	H	Q3s
2943	Q1m	H	H	Q3t
2944	Q1m	H	H	Q3u
2945	Q1m	H	Me	Q3r
2946	Q1m	H	Me	Q3s
2947	Q1m	H	Me	Q3t
2948	Q1m	H	Me	Q3u
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2950	Q1m	Me	H	Q3s
2951	Q1m	Me	H	Q3t
2952	Q1m	Me	H	Q3u
2953	Q1m	Me	Me	Q3r
2954	Q1m	Me	Me	Q3s
2955	Q1m	Me	Me	Q3t
2956	Q1m	Me	Me	Q3u
2957	Q1m	CF3	H	Q3r
2958	Q1m	CF3	H	Q3s
2959	Q1m	CF3	H	Q3t
2960	Q1m	CF3	H	Q3u
2961	Q1m	CF3	Me	Q3r
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2963	Q1m	CF3	Me	Q3t
2964	Q1m	CF3	Me	Q3u
2965	Q1n	H	H	Q3r
2966	Q1n	H	H	Q3s
2967	Q1n	H	H	Q3t
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2972	Q1n	H	Me	Q3u
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2974	Q1n	Me	H	Q3s
2975	Q1n	Me	H	Q3t
2976	Q1n	Me	H	Q3u
2977	Q1n	Me	Me	Q3r
2978	Q1n	Me	Me	Q3s
2979	Q1n	Me	Me	Q3t
2980	Q1n	Me	Me	Q3u
2981	Q1n	CF3	H	Q3r
2982	Q1n	CF3	H	Q3s
2983	Q1n	CF3	H	Q3t
2984	Q1n	CF3	H	Q3u
2985	Q1n	CF3	Me	Q3r
2986	Q1n	CF3	Me	Q3s
2987	Q1n	CF3	Me	Q3t
2988	Q1n	CF3	Me	Q3u
2989	Q1o	H	H	Q3r
2990	Q1o	H	H	Q3s
2991	Q1o	H	H	Q3t
2992	Q1o	H	H	Q3u
2993	Q1o	H	Me	Q3r
2994	Q1o	H	Me	Q3s
2995	Q1o	H	Me	Q3t
2996	Q1o	H	Me	Q3u
2997	Q1o	Me	H	Q3r
2998	Q1o	Me	H	Q3s
2999	Q1o	Me	H	Q3t
3000	Q1o	Me	H	Q3u
3001	Q1o	Me	Me	Q3r
3002	Q1o	Me	Me	Q3s
3003	Q1o	Me	Me	Q3t
3004	Q1o	Me	Me	Q3u
3005	Q1o	CF3	H	Q3r
3006	Q1o	CF3	H	Q3s
3007	Q1o	CF3	H	Q3t
3008	Q1o	CF3	H	Q3u
3009	Q1o	CF3	Me	Q3r
3010	Q1o	CF3	Me	Q3s
3011	Q1o	CF3	Me	Q3t
3012	Q1o	CF3	Me	Q3u
3013	Q1p	H	H	Q3r

3014	Q1p	H	H	Q3s
3015	Q1p	H	H	Q3t
3016	Q1p	H	H	Q3u
3017	Q1p	H	Me	Q3r
3018	Q1p	H	Me	Q3s
3019	Q1p	H	Me	Q3t
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3023	Q1p	Me	H	Q3t
3024	Q1p	Me	H	Q3u
3025	Q1p	Me	Me	Q3r
3026	Q1p	Me	Me	Q3s
3027	Q1p	Me	Me	Q3t
3028	Q1p	Me	Me	Q3u
3029	Q1p	CF3	H	Q3r
3030	Q1p	CF3	H	Q3s
3031	Q1p	CF3	H	Q3t
3032	Q1p	CF3	H	Q3u
3033	Q1p	CF3	Me	Q3r
3034	Q1p	CF3	Me	Q3s
3035	Q1p	CF3	Me	Q3t
3036	Q1p	CF3	Me	Q3u
3037	Q1q	H	H	Q3r
3038	Q1q	H	H	Q3s
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3097	Q1s	Me	Me	Q3r
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3103	Q1s	CF3	H	Q3t

3104	Q1s	CF3	H	Q3u
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3106	Q1s	CF3	Me	Q3s
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3108	Q1s	CF3	Me	Q3u
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3112	Q1t	H	H	Q3u
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3169	Q1v	Me	Me	Q3r
3170	Q1v	Me	Me	Q3s
3171	Q1v	Me	Me	Q3t
3172	Q1v	Me	Me	Q3u
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3174	Q1v	CF3	H	Q3s
3175	Q1v	CF3	H	Q3t
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3190	Q1w	Me	H	Q3s
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3196	Q1w	Me	Me	Q3u
3197	Q1w	CF3	H	Q3r
3198	Q1w	CF3	H	Q3s
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3200	Q1w	CF3	H	Q3u
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3204	Q1w	CF3	Me	Q3u
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3209	Q1x	H	Me	Q3r
3210	Q1x	H	Me	Q3s
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3218	Q1x	Me	Me	Q3s
3219	Q1x	Me	Me	Q3t
3220	Q1x	Me	Me	Q3u
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3222	Q1x	CF3	H	Q3s
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3224	Q1x	CF3	H	Q3u
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3227	Q1x	CF3	Me	Q3t
3228	Q1x	CF3	Me	Q3u
3229	Q1y	H	H	Q3r
3230	Q1y	H	H	Q3s
3231	Q1y	H	H	Q3t
3232	Q1y	H	H	Q3u
3233	Q1y	H	Me	Q3r
3234	Q1y	H	Me	Q3s
3235	Q1y	H	Me	Q3t
3236	Q1y	H	Me	Q3u
3237	Q1y	Me	H	Q3r
3238	Q1y	Me	H	Q3s

3239	Q1y	Me	H	Q3t
3240	Q1y	Me	H	Q3u
3241	Q1y	Me	Me	Q3r
3242	Q1y	Me	Me	Q3s
3243	Q1y	Me	Me	Q3t
3244	Q1y	Me	Me	Q3u
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3256	Q1z	H	H	Q3u
3257	Q1z	H	Me	Q3r
3258	Q1z	H	Me	Q3s
3259	Q1z	H	Me	Q3t
3260	Q1z	H	Me	Q3u
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3265	Q1z	Me	Me	Q3r
3266	Q1z	Me	Me	Q3s
3267	Q1z	Me	Me	Q3t
3268	Q1z	Me	Me	Q3u
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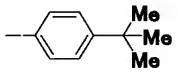
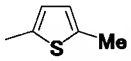
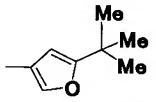
3270	Q1z	CF3	H	Q3s
3271	Q1z	CF3	H	Q3t
3272	Q1z	CF3	H	Q3u
3273	Q1z	CF3	Me	Q3r
3274	Q1z	CF3	Me	Q3s
3275	Q1z	CF3	Me	Q3t
3276	Q1z	CF3	Me	Q3u

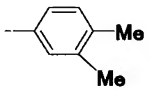
131) The compounds wherein R^1, R^2, R^3 and R^4 are any of the following combinations in Table 2, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof. The symbols in Table 2 denote the following substituents.

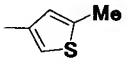
【Ka 1:】

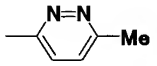
Q1a = 

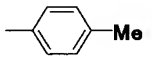
Q1j = 

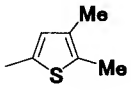
Q1s= 

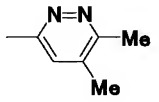
Q1b = 

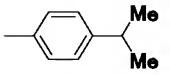
Q1k= 

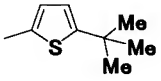
Q1t= 

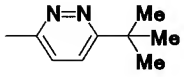
Q1c = 

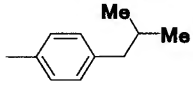
Q1l = 

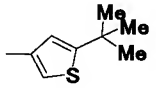
Q1u = 

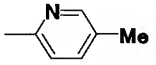
Q1d = 

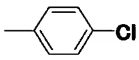
Q1m = 

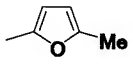
Q1v= 

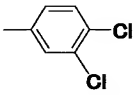
Q1e = 

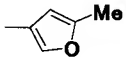
Q1n = 

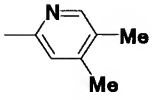
Q1w= 

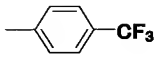
Q1f = 

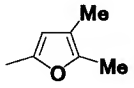
Q1o = 

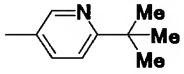
Q1g = 

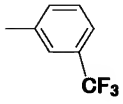
Q1p= 

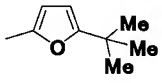
Q1x= 

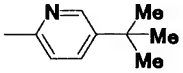
Q1h = 

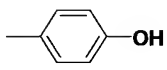
Q1q= 

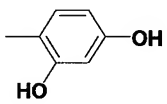
Q1y= 

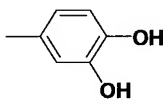
Q1i = 

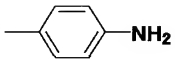
Q1r= 

Q1z= 

Q3v= 

Q3w= 

Q3x= 

Q3y= 

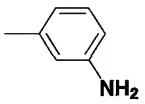
Q3z= 

Table 2

No	R^1	R^2	R^3	R^4
1	Q1a	H	H	Q3v
2	Q1a	H	H	Q3w
3	Q1a	H	H	Q3x
4	Q1a	H	H	Q3y
5	Q1a	H	H	Q3z
6	Q1a	H	Me	Q3v
7	Q1a	H	Me	Q3w
8	Q1a	H	Me	Q3x
9	Q1a	H	Me	Q3y
10	Q1a	H	Me	Q3z
11	Q1a	Me	H	Q3v
12	Q1a	Me	H	Q3w
13	Q1a	Me	H	Q3x
14	Q1a	Me	H	Q3y
15	Q1a	Me	H	Q3z
16	Q1a	Me	Me	Q3v
17	Q1a	Me	Me	Q3w
18	Q1a	Me	Me	Q3x
19	Q1a	Me	Me	Q3y
20	Q1a	Me	Me	Q3z
21	Q1a	CF3	H	Q3v
22	Q1a	CF3	H	Q3w
23	Q1a	CF3	H	Q3x
24	Q1a	CF3	H	Q3y
25	Q1a	CF3	H	Q3z
26	Q1a	CF3	Me	Q3v
27	Q1a	CF3	Me	Q3w
28	Q1a	CF3	Me	Q3x
29	Q1a	CF3	Me	Q3y
30	Q1a	CF3	Me	Q3z
31	Q1b	H	H	Q3v
32	Q1b	H	H	Q3w
33	Q1b	H	H	Q3x
34	Q1b	H	H	Q3y
35	Q1b	H	H	Q3z
36	Q1b	H	Me	Q3v
37	Q1b	H	Me	Q3w
38	Q1b	H	Me	Q3x
39	Q1b	H	Me	Q3y
40	Q1b	H	Me	Q3z
41	Q1b	Me	H	Q3v
42	Q1b	Me	H	Q3w
43	Q1b	Me	H	Q3x

44	Q1b	Me	H	Q3y
45	Q1b	Me	H	Q3z
46	Q1b	Me	Me	Q3v
47	Q1b	Me	Me	Q3w
48	Q1b	Me	Me	Q3x
49	Q1b	Me	Me	Q3y
50	Q1b	Me	Me	Q3z
51	Q1b	CF3	H	Q3v
52	Q1b	CF3	H	Q3w
53	Q1b	CF3	H	Q3x
54	Q1b	CF3	H	Q3y
55	Q1b	CF3	H	Q3z
56	Q1b	CF3	Me	Q3v
57	Q1b	CF3	Me	Q3w
58	Q1b	CF3	Me	Q3x
59	Q1b	CF3	Me	Q3y
60	Q1b	CF3	Me	Q3z
61	Q1c	H	H	Q3v
62	Q1c	H	H	Q3w
63	Q1c	H	H	Q3x
64	Q1c	H	H	Q3y
65	Q1c	H	H	Q3z
66	Q1c	H	Me	Q3v
67	Q1c	H	Me	Q3w
68	Q1c	H	Me	Q3x
69	Q1c	H	Me	Q3y
70	Q1c	H	Me	Q3z
71	Q1c	Me	H	Q3v
72	Q1c	Me	H	Q3w
73	Q1c	Me	H	Q3x
74	Q1c	Me	H	Q3y
75	Q1c	Me	H	Q3z
76	Q1c	Me	Me	Q3v
77	Q1c	Me	Me	Q3w
78	Q1c	Me	Me	Q3x
79	Q1c	Me	Me	Q3y
80	Q1c	Me	Me	Q3z
81	Q1c	CF3	H	Q3v
82	Q1c	CF3	H	Q3w
83	Q1c	CF3	H	Q3x
84	Q1c	CF3	H	Q3y
85	Q1c	CF3	H	Q3z
86	Q1c	CF3	Me	Q3v
87	Q1c	CF3	Me	Q3w
88	Q1c	CF3	Me	Q3x

89	Q1c	CF3	Me	Q3y
90	Q1c	CF3	Me	Q3z
91	Q1d	H	H	Q3v
92	Q1d	H	H	Q3w
93	Q1d	H	H	Q3x
94	Q1d	H	H	Q3y
95	Q1d	H	H	Q3z
96	Q1d	H	Me	Q3v
97	Q1d	H	Me	Q3w
98	Q1d	H	Me	Q3x
99	Q1d	H	Me	Q3y
100	Q1d	H	Me	Q3z
101	Q1d	Me	H	Q3v
102	Q1d	Me	H	Q3w
103	Q1d	Me	H	Q3x
104	Q1d	Me	H	Q3y
105	Q1d	Me	H	Q3z
106	Q1d	Me	Me	Q3v
107	Q1d	Me	Me	Q3w
108	Q1d	Me	Me	Q3x
109	Q1d	Me	Me	Q3y
110	Q1d	Me	Me	Q3z
111	Q1d	CF3	H	Q3v
112	Q1d	CF3	H	Q3w
113	Q1d	CF3	H	Q3x
114	Q1d	CF3	H	Q3y
115	Q1d	CF3	H	Q3z
116	Q1d	CF3	Me	Q3v
117	Q1d	CF3	Me	Q3w
118	Q1d	CF3	Me	Q3x
119	Q1d	CF3	Me	Q3y
120	Q1d	CF3	Me	Q3z
121	Q1e	H	H	Q3v
122	Q1e	H	H	Q3w
123	Q1e	H	H	Q3x
124	Q1e	H	H	Q3y
125	Q1e	H	H	Q3z
126	Q1e	H	Me	Q3v
127	Q1e	H	Me	Q3w
128	Q1e	H	Me	Q3x
129	Q1e	H	Me	Q3y
130	Q1e	H	Me	Q3z
131	Q1e	Me	H	Q3v
132	Q1e	Me	H	Q3w
133	Q1e	Me	H	Q3x

134	Q1e	Me	H	Q3y
135	Q1e	Me	H	Q3z
136	Q1e	Me	Me	Q3v
137	Q1e	Me	Me	Q3w
138	Q1e	Me	Me	Q3x
139	Q1e	Me	Me	Q3y
140	Q1e	Me	Me	Q3z
141	Q1e	CF3	H	Q3v
142	Q1e	CF3	H	Q3w
143	Q1e	CF3	H	Q3x
144	Q1e	CF3	H	Q3y
145	Q1e	CF3	H	Q3z
146	Q1e	CF3	Me	Q3v
147	Q1e	CF3	Me	Q3w
148	Q1e	CF3	Me	Q3x
149	Q1e	CF3	Me	Q3y
150	Q1e	CF3	Me	Q3z
151	Q1f	H	H	Q3v
152	Q1f	H	H	Q3w
153	Q1f	H	H	Q3x
154	Q1f	H	H	Q3y
155	Q1f	H	H	Q3z
156	Q1f	H	Me	Q3v
157	Q1f	H	Me	Q3w
158	Q1f	H	Me	Q3x
159	Q1f	H	Me	Q3y
160	Q1f	H	Me	Q3z
161	Q1f	Me	H	Q3v
162	Q1f	Me	H	Q3w
163	Q1f	Me	H	Q3x
164	Q1f	Me	H	Q3y
165	Q1f	Me	H	Q3z
166	Q1f	Me	Me	Q3v
167	Q1f	Me	Me	Q3w
168	Q1f	Me	Me	Q3x
169	Q1f	Me	Me	Q3y
170	Q1f	Me	Me	Q3z
171	Q1f	CF3	H	Q3v
172	Q1f	CF3	H	Q3w
173	Q1f	CF3	H	Q3x
174	Q1f	CF3	H	Q3y
175	Q1f	CF3	H	Q3z
176	Q1f	CF3	Me	Q3v
177	Q1f	CF3	Me	Q3w
178	Q1f	CF3	Me	Q3x

179	Q1f	CF3	Me	Q3y
180	Q1f	CF3	Me	Q3z
181	Q1g	H	H	Q3v
182	Q1g	H	H	Q3w
183	Q1g	H	H	Q3x
184	Q1g	H	H	Q3y
185	Q1g	H	H	Q3z
186	Q1g	H	Me	Q3v
187	Q1g	H	Me	Q3w
188	Q1g	H	Me	Q3x
189	Q1g	H	Me	Q3y
190	Q1g	H	Me	Q3z
191	Q1g	Me	H	Q3v
192	Q1g	Me	H	Q3w
193	Q1g	Me	H	Q3x
194	Q1g	Me	H	Q3y
195	Q1g	Me	H	Q3z
196	Q1g	Me	Me	Q3v
197	Q1g	Me	Me	Q3w
198	Q1g	Me	Me	Q3x
199	Q1g	Me	Me	Q3y
200	Q1g	Me	Me	Q3z
201	Q1g	CF3	H	Q3v
202	Q1g	CF3	H	Q3w
203	Q1g	CF3	H	Q3x
204	Q1g	CF3	H	Q3y
205	Q1g	CF3	H	Q3z
206	Q1g	CF3	Me	Q3v
207	Q1g	CF3	Me	Q3w
208	Q1g	CF3	Me	Q3x
209	Q1g	CF3	Me	Q3y
210	Q1g	CF3	Me	Q3z
211	Q1h	H	H	Q3v
212	Q1h	H	H	Q3w
213	Q1h	H	H	Q3x
214	Q1h	H	H	Q3y
215	Q1h	H	H	Q3z
216	Q1h	H	Me	Q3v
217	Q1h	H	Me	Q3w
218	Q1h	H	Me	Q3x
219	Q1h	H	Me	Q3y
220	Q1h	H	Me	Q3z
221	Q1h	Me	H	Q3v
222	Q1h	Me	H	Q3w
223	Q1h	Me	H	Q3x

224	Q1h	Me	H	Q3y
225	Q1h	Me	H	Q3z
226	Q1h	Me	Me	Q3v
227	Q1h	Me	Me	Q3w
228	Q1h	Me	Me	Q3x
229	Q1h	Me	Me	Q3y
230	Q1h	Me	Me	Q3z
231	Q1h	CF3	H	Q3v
232	Q1h	CF3	H	Q3w
233	Q1h	CF3	H	Q3x
234	Q1h	CF3	H	Q3y
235	Q1h	CF3	H	Q3z
236	Q1h	CF3	Me	Q3v
237	Q1h	CF3	Me	Q3w
238	Q1h	CF3	Me	Q3x
239	Q1h	CF3	Me	Q3y
240	Q1h	CF3	Me	Q3z
241	Q1i	H	H	Q3v
242	Q1i	H	H	Q3w
243	Q1i	H	H	Q3x
244	Q1i	H	H	Q3y
245	Q1i	H	H	Q3z
246	Q1i	H	Me	Q3v
247	Q1i	H	Me	Q3w
248	Q1i	H	Me	Q3x
249	Q1i	H	Me	Q3y
250	Q1i	H	Me	Q3z
251	Q1i	Me	H	Q3v
252	Q1i	Me	H	Q3w
253	Q1i	Me	H	Q3x
254	Q1i	Me	H	Q3y
255	Q1i	Me	H	Q3z
256	Q1i	Me	Me	Q3v
257	Q1i	Me	Me	Q3w
258	Q1i	Me	Me	Q3x
259	Q1i	Me	Me	Q3y
260	Q1i	Me	Me	Q3z
261	Q1i	CF3	H	Q3v
262	Q1i	CF3	H	Q3w
263	Q1i	CF3	H	Q3x
264	Q1i	CF3	H	Q3y
265	Q1i	CF3	H	Q3z
266	Q1I	CF3	Me	Q3v
267	Q1I	CF3	Me	Q3w
268	Q1I	CF3	Me	Q3X

269	Q1I	CF3	Me	Q3y
270	Q1I	CF3	Me	Q3z
271	Q1j	H	H	Q3v
272	Q1j	H	H	Q3w
273	Q1j	H	H	Q3X
274	Q1j	H	H	Q3y
275	Q1j	H	H	Q3z
276	Q1j	H	Me	Q3v
277	Q1j	H	Me	Q3w
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279	Q1j	H	Me	Q3y
280	Q1j	H	Me	Q3z
281	Q1j	Me	H	Q3v
282	Q1j	Me	H	Q3w
283	Q1j	Me	H	Q3x
284	Q1j	Me	H	Q3y
285	Q1j	Me	H	Q3z
286	Q1j	Me	Me	Q3v
287	Q1j	Me	Me	Q3w
288	Q1j	Me	Me	Q3x
289	Q1j	Me	Me	Q3y
290	Q1j	Me	Me	Q3z
291	Q1j	CF3	H	Q3v
292	Q1j	CF3	H	Q3w
293	Q1j	CF3	H	Q3x
294	Q1j	CF3	H	Q3y
295	Q1j	CF3	H	Q3z
296	Q1j	CF3	Me	Q3v
297	Q1j	CF3	Me	Q3w
298	Q1j	CF3	Me	Q3x
299	Q1j	CF3	Me	Q3y
300	Q1j	CF3	Me	Q3z
301	Q1k	H	H	Q3v
302	Q1k	H	H	Q3w
303	Q1k	H	H	Q3x
304	Q1k	H	H	Q3y
305	Q1k	H	H	Q3z
306	Q1k	H	Me	Q3v
307	Q1k	H	Me	Q3w
308	Q1k	H	Me	Q3x
309	Q1k	H	Me	Q3y
310	Q1k	H	Me	Q3z
311	Q1k	Me	H	Q3v
312	Q1k	Me	H	Q3w
313	Q1k	Me	H	Q3x

314	Q1k	Me	H	Q3y
315	Q1k	Me	H	Q3z
316	Q1k	Me	Me	Q3v
317	Q1k	Me	Me	Q3w
318	Q1k	Me	Me	Q3x
319	Q1k	Me	Me	Q3y
320	Q1k	Me	Me	Q3z
321	Q1k	CF3	H	Q3v
322	Q1k	CF3	H	Q3w
323	Q1k	CF3	H	Q3x
324	Q1k	CF3	H	Q3y
325	Q1k	CF3	H	Q3z
326	Q1k	CF3	Me	Q3v
327	Q1k	CF3	Me	Q3w
328	Q1k	CF3	Me	Q3x
329	Q1k	CF3	Me	Q3y
330	Q1k	CF3	Me	Q3z
331	Q1l	H	H	Q3v
332	Q1l	H	H	Q3w
333	Q1l	H	H	Q3x
334	Q1l	H	H	Q3y
335	Q1l	H	H	Q3z
336	Q1l	H	Me	Q3v
337	Q1l	H	Me	Q3w
338	Q1l	H	Me	Q3x
339	Q1l	H	Me	Q3y
340	Q1l	H	Me	Q3z
341	Q1l	Me	H	Q3v
342	Q1l	Me	H	Q3w
343	Q1l	Me	H	Q3x
344	Q1l	Me	H	Q3y
345	Q1l	Me	H	Q3z
346	Q1l	Me	Me	Q3v
347	Q1l	Me	Me	Q3w
348	Q1l	Me	Me	Q3x
349	Q1l	Me	Me	Q3y
350	Q1l	Me	Me	Q3z
351	Q1l	CF3	H	Q3v
352	Q1l	CF3	H	Q3w
353	Q1l	CF3	H	Q3x
354	Q1l	CF3	H	Q3y
355	Q1l	CF3	H	Q3z
356	Q1l	CF3	Me	Q3v
357	Q1l	CF3	Me	Q3w
358	Q1l	CF3	Me	Q3x

359	Q1l	CF3	Me	Q3y
360	Q1l	CF3	Me	Q3z
361	Q1m	H	H	Q3v
362	Q1m	H	H	Q3w
363	Q1m	H	H	Q3x
364	Q1m	H	H	Q3y
365	Q1m	H	H	Q3z
366	Q1m	H	Me	Q3v
367	Q1m	H	Me	Q3w
368	Q1m	H	Me	Q3x
369	Q1m	H	Me	Q3y
370	Q1m	H	Me	Q3z
371	Q1m	Me	H	Q3v
372	Q1m	Me	H	Q3w
373	Q1m	Me	H	Q3x
374	Q1m	Me	H	Q3y
375	Q1m	Me	H	Q3z
376	Q1m	Me	Me	Q3v
377	Q1m	Me	Me	Q3w
378	Q1m	Me	Me	Q3x
379	Q1m	Me	Me	Q3y
380	Q1m	Me	Me	Q3z
381	Q1m	CF3	H	Q3v
382	Q1m	CF3	H	Q3w
383	Q1m	CF3	H	Q3x
384	Q1m	CF3	H	Q3y
385	Q1m	CF3	H	Q3z
386	Q1m	CF3	Me	Q3v
387	Q1m	CF3	Me	Q3w
388	Q1m	CF3	Me	Q3x
389	Q1m	CF3	Me	Q3y
390	Q1m	CF3	Me	Q3z
391	Q1n	H	H	Q3v
392	Q1n	H	H	Q3w
393	Q1n	H	H	Q3x
394	Q1n	H	H	Q3y
395	Q1n	H	H	Q3z
396	Q1n	H	Me	Q3v
397	Q1n	H	Me	Q3w
398	Q1n	H	Me	Q3x
399	Q1n	H	Me	Q3y
400	Q1n	H	Me	Q3z
401	Q1n	Me	H	Q3v
402	Q1n	Me	H	Q3w
403	Q1n	Me	H	Q3x

404	Q1n	Me	H	Q3y
405	Q1n	Me	H	Q3z
406	Q1n	Me	Me	Q3v
407	Q1n	Me	Me	Q3w
408	Q1n	Me	Me	Q3x
409	Q1n	Me	Me	Q3y
410	Q1n	Me	Me	Q3z
411	Q1n	CF3	H	Q3v
412	Q1n	CF3	H	Q3w
413	Q1n	CF3	H	Q3x
414	Q1n	CF3	H	Q3y
415	Q1n	CF3	H	Q3z
416	Q1n	CF3	Me	Q3v
417	Q1n	CF3	Me	Q3w
418	Q1n	CF3	Me	Q3x
419	Q1n	CF3	Me	Q3y
420	Q1n	CF3	Me	Q3z
421	Q1o	H	H	Q3v
422	Q1o	H	H	Q3w
423	Q1o	H	H	Q3x
424	Q1o	H	H	Q3y
425	Q1o	H	H	Q3z
426	Q1o	H	Me	Q3v
427	Q1o	H	Me	Q3w
428	Q1o	H	Me	Q3x
429	Q1o	H	Me	Q3y
430	Q1o	H	Me	Q3z
431	Q1o	Me	H	Q3v
432	Q1o	Me	H	Q3w
433	Q1o	Me	H	Q3x
434	Q1o	Me	H	Q3y
435	Q1o	Me	H	Q3z
436	Q1o	Me	Me	Q3v
437	Q1o	Me	Me	Q3w
438	Q1o	Me	Me	Q3x
439	Q1o	Me	Me	Q3y
440	Q1o	Me	Me	Q3z
441	Q1o	CF3	H	Q3v
442	Q1o	CF3	H	Q3w
443	Q1o	CF3	H	Q3x
444	Q1o	CF3	H	Q3y
445	Q1o	CF3	H	Q3z
446	Q1o	CF3	Me	Q3v
447	Q1o	CF3	Me	Q3w
448	Q1o	CF3	Me	Q3x

449	Q1o	CF3	Me	Q3y
450	Q1o	CF3	Me	Q3z
451	Q1p	H	H	Q3v
452	Q1p	H	H	Q3w
453	Q1p	H	H	Q3x
454	Q1p	H	H	Q3y
455	Q1p	H	H	Q3z
456	Q1p	H	Me	Q3v
457	Q1p	H	Me	Q3w
458	Q1p	H	Me	Q3x
459	Q1p	H	Me	Q3y
460	Q1p	H	Me	Q3z
461	Q1p	Me	H	Q3v
462	Q1p	Me	H	Q3w
463	Q1p	Me	H	Q3x
464	Q1p	Me	H	Q3y
465	Q1p	Me	H	Q3z
466	Q1p	Me	Me	Q3v
467	Q1p	Me	Me	Q3w
468	Q1p	Me	Me	Q3x
469	Q1p	Me	Me	Q3y
470	Q1p	Me	Me	Q3z
471	Q1p	CF3	H	Q3v
472	Q1p	CF3	H	Q3w
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474	Q1p	CF3	H	Q3y
475	Q1p	CF3	H	Q3z
476	Q1p	CF3	Me	Q3v
477	Q1p	CF3	Me	Q3w
478	Q1p	CF3	Me	Q3x
479	Q1p	CF3	Me	Q3y
480	Q1p	CF3	Me	Q3z
481	Q1q	H	H	Q3v
482	Q1q	H	H	Q3w
483	Q1q	H	H	Q3x
484	Q1q	H	H	Q3y
485	Q1q	H	H	Q3z
486	Q1q	H	Me	Q3v
487	Q1q	H	Me	Q3w
488	Q1q	H	Me	Q3x
489	Q1q	H	Me	Q3y
490	Q1q	H	Me	Q3z
491	Q1q	Me	H	Q3v
492	Q1q	Me	H	Q3w
493	Q1q	Me	H	Q3x

494	Q1q	Me	H	Q3y
495	Q1q	Me	H	Q3z
496	Q1q	Me	Me	Q3v
497	Q1q	Me	Me	Q3w
498	Q1q	Me	Me	Q3x
499	Q1q	Me	Me	Q3y
500	Q1q	Me	Me	Q3z
501	Q1q	CF3	H	Q3v
502	Q1q	CF3	H	Q3w
503	Q1q	CF3	H	Q3x
504	Q1q	CF3	H	Q3y
505	Q1q	CF3	H	Q3z
506	Q1q	CF3	Me	Q3v
507	Q1q	CF3	Me	Q3w
508	Q1q	CF3	Me	Q3x
509	Q1q	CF3	Me	Q3y
510	Q1q	CF3	Me	Q3z
511	Q1r	H	H	Q3v
512	Q1r	H	H	Q3w
513	Q1r	H	H	Q3x
514	Q1r	H	H	Q3y
515	Q1r	H	H	Q3z
516	Q1r	H	Me	Q3v
517	Q1r	H	Me	Q3w
518	Q1r	H	Me	Q3x
519	Q1r	H	Me	Q3y
520	Q1r	H	Me	Q3z
521	Q1r	Me	H	Q3v
522	Q1r	Me	H	Q3w
523	Q1r	Me	H	Q3x
524	Q1r	Me	H	Q3y
525	Q1r	Me	H	Q3z
526	Q1r	Me	Me	Q3v
527	Q1r	Me	Me	Q3w
528	Q1r	Me	Me	Q3x
529	Q1r	Me	Me	Q3y
530	Q1r	Me	Me	Q3z
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532	Q1r	CF3	H	Q3w
533	Q1r	CF3	H	Q3x
534	Q1r	CF3	H	Q3y
535	Q1r	CF3	H	Q3z
536	Q1r	CF3	Me	Q3v
537	Q1r	CF3	Me	Q3w
538	Q1r	CF3	Me	Q3x

539	Q1r	CF3	Me	Q3y
540	Q1r	CF3	Me	Q3z
541	Q1s	H	H	Q3v
542	Q1s	H	H	Q3w
543	Q1s	H	H	Q3x
544	Q1s	H	H	Q3y
545	Q1s	H	H	Q3z
546	Q1s	H	Me	Q3v
547	Q1s	H	Me	Q3w
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549	Q1s	H	Me	Q3y
550	Q1s	H	Me	Q3z
551	Q1s	Me	H	Q3v
552	Q1s	Me	H	Q3w
553	Q1s	Me	H	Q3x
554	Q1s	Me	H	Q3y
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556	Q1s	Me	Me	Q3v
557	Q1s	Me	Me	Q3w
558	Q1s	Me	Me	Q3x
559	Q1s	Me	Me	Q3y
560	Q1s	Me	Me	Q3z
561	Q1s	CF3	H	Q3v
562	Q1s	CF3	H	Q3w
563	Q1s	CF3	H	Q3x
564	Q1s	CF3	H	Q3y
565	Q1s	CF3	H	Q3z
566	Q1s	CF3	Me	Q3v
567	Q1s	CF3	Me	Q3w
568	Q1s	CF3	Me	Q3x
569	Q1s	CF3	Me	Q3y
570	Q1s	CF3	Me	Q3z
571	Q1t	H	H	Q3v
572	Q1t	H	H	Q3w
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574	Q1t	H	H	Q3y
575	Q1t	H	H	Q3z
576	Q1t	H	Me	Q3v
577	Q1t	H	Me	Q3w
578	Q1t	H	Me	Q3x
579	Q1t	H	Me	Q3y
580	Q1t	H	Me	Q3z
581	Q1t	Me	H	Q3v
582	Q1t	Me	H	Q3w
583	Q1t	Me	H	Q3x

584	Q1t	Me	H	Q3y
585	Q1t	Me	H	Q3z
586	Q1t	Me	Me	Q3v
587	Q1t	Me	Me	Q3w
588	Q1t	Me	Me	Q3x
589	Q1t	Me	Me	Q3y
590	Q1t	Me	Me	Q3z
591	Q1t	CF3	H	Q3v
592	Q1t	CF3	H	Q3w
593	Q1t	CF3	H	Q3x
594	Q1t	CF3	H	Q3y
595	Q1t	CF3	H	Q3z
596	Q1t	CF3	Me	Q3v
597	Q1t	CF3	Me	Q3w
598	Q1t	CF3	Me	Q3x
599	Q1t	CF3	Me	Q3y
600	Q1t	CF3	Me	Q3z
601	Q1u	H	H	Q3v
602	Q1u	H	H	Q3w
603	Q1u	H	H	Q3x
604	Q1u	H	H	Q3y
605	Q1u	H	H	Q3z
606	Q1u	H	Me	Q3v
607	Q1u	H	Me	Q3w
608	Q1u	H	Me	Q3x
609	Q1u	H	Me	Q3y
610	Q1u	H	Me	Q3z
611	Q1u	Me	H	Q3v
612	Q1u	Me	H	Q3w
613	Q1u	Me	H	Q3x
614	Q1u	Me	H	Q3y
615	Q1u	Me	H	Q3z
616	Q1u	Me	Me	Q3v
617	Q1u	Me	Me	Q3w
618	Q1u	Me	Me	Q3x
619	Q1u	Me	Me	Q3y
620	Q1u	Me	Me	Q3z
621	Q1u	CF3	H	Q3v
622	Q1u	CF3	H	Q3w
623	Q1u	CF3	H	Q3x
624	Q1u	CF3	H	Q3y
625	Q1u	CF3	H	Q3z
626	Q1u	CF3	Me	Q3v
627	Q1u	CF3	Me	Q3w
628	Q1u	CF3	Me	Q3x

629	Q1u	CF3	Me	Q3y
630	Q1u	CF3	Me	Q3z
631	Q1v	H	H	Q3v
632	Q1v	H	H	Q3w
633	Q1v	H	H	Q3x
634	Q1v	H	H	Q3y
635	Q1v	H	H	Q3z
636	Q1v	H	Me	Q3v
637	Q1v	H	Me	Q3w
638	Q1v	H	Me	Q3x
639	Q1v	H	Me	Q3y
640	Q1v	H	Me	Q3z
641	Q1v	Me	H	Q3v
642	Q1v	Me	H	Q3w
643	Q1v	Me	H	Q3x
644	Q1v	Me	H	Q3y
645	Q1v	Me	H	Q3z
646	Q1v	Me	Me	Q3v
647	Q1v	Me	Me	Q3w
648	Q1v	Me	Me	Q3x
649	Q1v	Me	Me	Q3y
650	Q1v	Me	Me	Q3z
651	Q1v	CF3	H	Q3v
652	Q1v	CF3	H	Q3w
653	Q1v	CF3	H	Q3x
654	Q1v	CF3	H	Q3y
655	Q1v	CF3	H	Q3z
656	Q1v	CF3	Me	Q3v
657	Q1v	CF3	Me	Q3w
658	Q1v	CF3	Me	Q3x
659	Q1v	CF3	Me	Q3y
660	Q1v	CF3	Me	Q3z
661	Q1w	H	H	Q3v
662	Q1w	H	H	Q3w
663	Q1w	H	H	Q3x
664	Q1w	H	H	Q3y
665	Q1w	H	H	Q3z
666	Q1w	H	Me	Q3v
667	Q1w	H	Me	Q3w
668	Q1w	H	Me	Q3x
669	Q1w	H	Me	Q3y
670	Q1w	H	Me	Q3z
671	Q1w	Me	H	Q3v
672	Q1w	Me	H	Q3w
673	Q1w	Me	H	Q3x

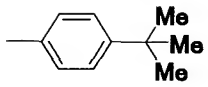
674	Q1w	Me	H	Q3y
675	Q1w	Me	H	Q3z
676	Q1w	Me	Me	Q3v
677	Q1w	Me	Me	Q3w
678	Q1w	Me	Me	Q3x
679	Q1w	Me	Me	Q3y
680	Q1w	Me	Me	Q3z
681	Q1w	CF3	H	Q3v
682	Q1w	CF3	H	Q3w
683	Q1w	CF3	H	Q3x
684	Q1w	CF3	H	Q3y
685	Q1w	CF3	H	Q3z
686	Q1w	CF3	Me	Q3v
687	Q1w	CF3	Me	Q3w
688	Q1w	CF3	Me	Q3x
689	Q1w	CF3	Me	Q3y
690	Q1w	CF3	Me	Q3z
691	Q1x	H	H	Q3v
692	Q1x	H	H	Q3w
693	Q1x	H	H	Q3x
694	Q1x	H	H	Q3y
695	Q1x	H	H	Q3z
696	Q1x	H	Me	Q3v
697	Q1x	H	Me	Q3w
698	Q1x	H	Me	Q3x
699	Q1x	H	Me	Q3y
700	Q1x	H	Me	Q3z
701	Q1x	Me	H	Q3v
702	Q1x	Me	H	Q3w
703	Q1x	Me	H	Q3x
704	Q1x	Me	H	Q3y
705	Q1x	Me	H	Q3z
706	Q1x	Me	Me	Q3v
707	Q1x	Me	Me	Q3w
708	Q1x	Me	Me	Q3x
709	Q1x	Me	Me	Q3y
710	Q1x	Me	Me	Q3z
711	Q1x	CF3	H	Q3v
712	Q1x	CF3	H	Q3w
713	Q1x	CF3	H	Q3x
714	Q1x	CF3	H	Q3y
715	Q1x	CF3	H	Q3z
716	Q1x	CF3	Me	Q3v
717	Q1x	CF3	Me	Q3w
718	Q1x	CF3	Me	Q3x

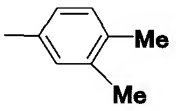
719	Q1x	CF3	Me	Q3y
720	Q1x	CF3	Me	Q3z
721	Q1y	H	H	Q3v
722	Q1y	H	H	Q3w
723	Q1y	H	H	Q3x
724	Q1y	H	H	Q3y
725	Q1y	H	H	Q3z
726	Q1y	H	Me	Q3v
727	Q1y	H	Me	Q3w
728	Q1y	H	Me	Q3x
729	Q1y	H	Me	Q3y
730	Q1y	H	Me	Q3z
731	Q1y	Me	H	Q3v
732	Q1y	Me	H	Q3w
733	Q1y	Me	H	Q3x
734	Q1y	Me	H	Q3y
735	Q1y	Me	H	Q3z
736	Q1y	Me	Me	Q3v
737	Q1y	Me	Me	Q3w
738	Q1y	Me	Me	Q3x
739	Q1y	Me	Me	Q3y
740	Q1y	Me	Me	Q3z
741	Q1y	CF3	H	Q3v
742	Q1y	CF3	H	Q3w
743	Q1y	CF3	H	Q3x
744	Q1y	CF3	H	Q3y
745	Q1y	CF3	H	Q3z
746	Q1y	CF3	Me	Q3v
747	Q1y	CF3	Me	Q3w
748	Q1y	CF3	Me	Q3x
749	Q1y	CF3	Me	Q3y
750	Q1y	CF3	Me	Q3z
751	Q1z	H	H	Q3v
752	Q1z	H	H	Q3w
753	Q1z	H	H	Q3x
754	Q1z	H	H	Q3y
755	Q1z	H	H	Q3z
756	Q1z	H	Me	Q3v
757	Q1z	H	Me	Q3w
758	Q1z	H	Me	Q3x
759	Q1z	H	Me	Q3y
760	Q1z	H	Me	Q3z
761	Q1z	Me	H	Q3v
762	Q1z	Me	H	Q3w
763	Q1z	Me	H	Q3x

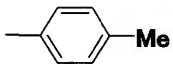
764	Q1z	Me	H	Q3y
765	Q1z	Me	H	Q3z
766	Q1z	Me	Me	Q3v
767	Q1z	Me	Me	Q3w
768	Q1z	Me	Me	Q3x
769	Q1z	Me	Me	Q3y
770	Q1z	Me	Me	Q3z
771	Q1z	CF3	H	Q3v
772	Q1z	CF3	H	Q3w
773	Q1z	CF3	H	Q3x
774	Q1z	CF3	H	Q3y
775	Q1z	CF3	H	Q3z
776	Q1z	CF3	Me	Q3v
777	Q1z	CF3	Me	Q3w
778	Q1z	CF3	Me	Q3x
779	Q1z	CF3	Me	Q3y
780	Q1z	CF3	Me	Q3z

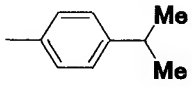
132) The compounds wherein R^7, R^8, R^9 and R^{10} are any of the following combinations in Table 3, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof. The symbols in Table 3 denote the following substituents.

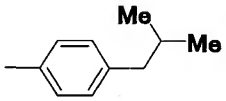
【Ka 12】

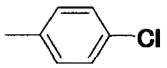
Q1a = 

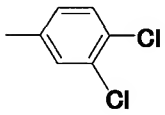
Q1b = 

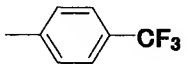
Q1c = 

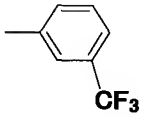
Q1d = 

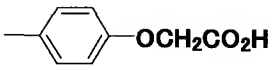
Q1e = 

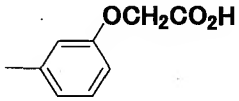
Q1f = 

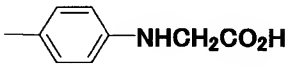
Q1g = 

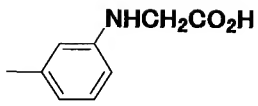
Q1h = 

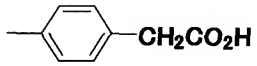
Q1i = 

A3a = 

A3b = 

A3c = 

A3d = 

A3e = 

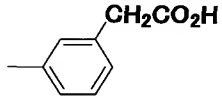
A3f = 

Table 3

No	R^7	R^8	R^9	R^{10}
1	Q1a	Me	Me	A3a
2	Q1a	Me	Me	A3b
3	Q1a	Me	Me	A3c
4	Q1a	Me	Me	A3d
5	Q1a	Me	Me	A3e
6	Q1a	Me	Me	A3f
7	Q1a	Me	H	A3a
8	Q1a	Me	H	A3b
9	Q1a	Me	H	A3c
10	Q1a	Me	H	A3d
11	Q1a	Me	H	A3e
12	Q1a	Me	H	A3f
13	Q1a	CF3	Me	A3a
14	Q1a	CF3	Me	A3b
15	Q1a	CF3	Me	A3c
16	Q1a	CF3	Me	A3d
17	Q1a	CF3	Me	A3e
18	Q1a	CF3	Me	A3f
19	Q1a	CF3	H	A3a
20	Q1a	CF3	H	A3b
21	Q1a	CF3	H	A3c
22	Q1a	CF3	H	A3d
23	Q1a	CF3	H	A3e
24	Q1a	CF3	H	A3f
25	Q1b	Me	Me	A3a
26	Q1b	Me	Me	A3b
27	Q1b	Me	Me	A3c
28	Q1b	Me	Me	A3d
29	Q1b	Me	Me	A3e
30	Q1b	Me	Me	A3f
31	Q1b	Me	H	A3a
32	Q1b	Me	H	A3b
33	Q1b	Me	H	A3c
34	Q1b	Me	H	A3d
35	Q1b	Me	H	A3e
36	Q1b	Me	H	A3f
37	Q1b	CF3	Me	A3a
38	Q1b	CF3	Me	A3b
39	Q1b	CF3	Me	A3c
40	Q1b	CF3	Me	A3d
41	Q1b	CF3	Me	A3e
42	Q1b	CF3	Me	A3f
43	Q1b	CF3	H	A3a

44	Q1b	CF3	H	A3b
45	Q1b	CF3	H	A3c
46	Q1b	CF3	H	A3d
47	Q1b	CF3	H	A3e
48	Q1b	CF3	H	A3f
49	Q1c	Me	Me	A3a
50	Q1c	Me	Me	A3b
51	Q1c	Me	Me	A3c
52	Q1c	Me	Me	A3d
53	Q1c	Me	Me	A3e
54	Q1c	Me	Me	A3f
55	Q1c	Me	H	A3a
56	Q1c	Me	H	A3b
57	Q1c	Me	H	A3c
58	Q1c	Me	H	A3d
59	Q1c	Me	H	A3e
60	Q1c	Me	H	A3f
61	Q1c	CF3	Me	A3a
62	Q1c	CF3	Me	A3b
63	Q1c	CF3	Me	A3c
64	Q1c	CF3	Me	A3d
65	Q1c	CF3	Me	A3e
66	Q1c	CF3	Me	A3f
67	Q1c	CF3	H	A3a
68	Q1c	CF3	H	A3b
69	Q1c	CF3	H	A3c
70	Q1c	CF3	H	A3d
71	Q1c	CF3	H	A3e
72	Q1c	CF3	H	A3f
73	Q1d	Me	Me	A3a
74	Q1d	Me	Me	A3b
75	Q1d	Me	Me	A3c
76	Q1d	Me	Me	A3d
77	Q1d	Me	Me	A3e
78	Q1d	Me	Me	A3f
79	Q1d	Me	H	A3a
80	Q1d	Me	H	A3b
81	Q1d	Me	H	A3c
82	Q1d	Me	H	A3d
83	Q1d	Me	H	A3e
84	Q1d	Me	H	A3f
85	Q1d	CF3	Me	A3a
86	Q1d	CF3	Me	A3b
87	Q1d	CF3	Me	A3c
88	Q1d	CF3	Me	A3d

89	Q1d	CF3	Me	A3e
90	Q1d	CF3	Me	A3f
91	Q1d	CF3	H	A3a
92	Q1d	CF3	H	A3b
93	Q1d	CF3	H	A3c
94	Q1d	CF3	H	A3d
95	Q1d	CF3	H	A3e
96	Q1d	CF3	H	A3f
97	Q1e	Me	Me	A3a
98	Q1e	Me	Me	A3b
99	Q1e	Me	Me	A3c
100	Q1e	Me	Me	A3d
101	Q1e	Me	Me	A3e
102	Q1e	Me	Me	A3f
103	Q1e	Me	H	A3a
104	Q1e	Me	H	A3b
105	Q1e	Me	H	A3c
106	Q1e	Me	H	A3d
107	Q1e	Me	H	A3e
108	Q1e	Me	H	A3f
109	Q1e	CF3	Me	A3a
110	Q1e	CF3	Me	A3b
111	Q1e	CF3	Me	A3c
112	Q1e	CF3	Me	A3d
113	Q1e	CF3	Me	A3e
114	Q1e	CF3	Me	A3f
115	Q1e	CF3	H	A3a
116	Q1e	CF3	H	A3b
117	Q1e	CF3	H	A3c
118	Q1e	CF3	H	A3d
119	Q1e	CF3	H	A3e
120	Q1e	CF3	H	A3f
121	Q1f	Me	Me	A3a
122	Q1f	Me	Me	A3b
123	Q1f	Me	Me	A3c
124	Q1f	Me	Me	A3d
125	Q1f	Me	Me	A3e
126	Q1f	Me	Me	A3f
127	Q1f	Me	H	A3a
128	Q1f	Me	H	A3b
129	Q1f	Me	H	A3c
130	Q1f	Me	H	A3d
131	Q1f	Me	H	A3e
132	Q1f	Me	H	A3f
133	Q1f	CF3	Me	A3a

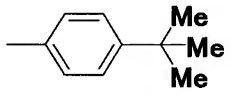
134	Q1f	CF3	Me	A3b
135	Q1f	CF3	Me	A3c
136	Q1f	CF3	Me	A3d
137	Q1f	CF3	Me	A3e
138	Q1f	CF3	Me	A3f
139	Q1f	CF3	H	A3a
140	Q1f	CF3	H	A3b
141	Q1f	CF3	H	A3c
142	Q1f	CF3	H	A3d
143	Q1f	CF3	H	A3e
144	Q1f	CF3	H	A3f
145	Q1g	Me	Me	A3a
146	Q1g	Me	Me	A3b
147	Q1g	Me	Me	A3c
148	Q1g	Me	Me	A3d
149	Q1g	Me	Me	A3e
150	Q1g	Me	Me	A3f
151	Q1g	Me	H	A3a
152	Q1g	Me	H	A3b
153	Q1g	Me	H	A3c
154	Q1g	Me	H	A3d
155	Q1g	Me	H	A3e
156	Q1g	Me	H	A3f
157	Q1g	CF3	Me	A3a
158	Q1g	CF3	Me	A3b
159	Q1g	CF3	Me	A3c
160	Q1g	CF3	Me	A3d
161	Q1g	CF3	Me	A3e
162	Q1g	CF3	Me	A3f
163	Q1g	CF3	H	A3a
164	Q1g	CF3	H	A3b
165	Q1g	CF3	H	A3c
166	Q1g	CF3	H	A3d
167	Q1g	CF3	H	A3e
168	Q1g	CF3	H	A3f
169	Q1h	Me	Me	A3a
170	Q1h	Me	Me	A3b
171	Q1h	Me	Me	A3c
172	Q1h	Me	Me	A3d
173	Q1h	Me	Me	A3e
174	Q1h	Me	Me	A3f
175	Q1h	Me	H	A3a
176	Q1h	Me	H	A3b
177	Q1h	Me	H	A3c
178	Q1h	Me	H	A3d

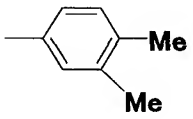
179	Q1h	Me	H	A3e
180	Q1h	Me	H	A3f
181	Q1h	CF3	Me	A3a
182	Q1h	CF3	Me	A3b
183	Q1h	CF3	Me	A3c
184	Q1h	CF3	Me	A3d
185	Q1h	CF3	Me	A3e
186	Q1h	CF3	Me	A3f
187	Q1h	CF3	H	A3a
188	Q1h	CF3	H	A3b
189	Q1h	CF3	H	A3c
190	Q1h	CF3	H	A3d
191	Q1h	CF3	H	A3e
192	Q1h	CF3	H	A3f
193	Q1i	Me	Me	A3a
194	Q1i	Me	Me	A3b
195	Q1i	Me	Me	A3c
196	Q1i	Me	Me	A3d
197	Q1i	Me	Me	A3e
198	Q1i	Me	Me	A3f
199	Q1i	Me	H	A3a
200	Q1i	Me	H	A3b
201	Q1i	Me	H	A3c
202	Q1i	Me	H	A3d
203	Q1i	Me	H	A3e
204	Q1i	Me	H	A3f
205	Q1i	CF3	Me	A3a
206	Q1i	CF3	Me	A3b
207	Q1i	CF3	Me	A3c
208	Q1i	CF3	Me	A3d
209	Q1i	CF3	Me	A3e
210	Q1i	CF3	Me	A3f
211	Q1i	CF3	H	A3a
212	Q1i	CF3	H	A3b
213	Q1i	CF3	H	A3c
214	Q1i	CF3	H	A3d
215	Q1i	CF3	H	A3e
216	Q1i	CF3	H	A3f

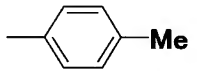
133) The compounds wherein R^{12}, R^{13}, R^{14} and R^{15} are any of the following combinations in Table 4, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or

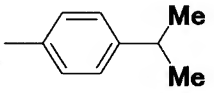
solvates thereof. The symbols in Table 4 denote the following substituents.

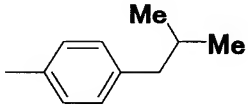
【Ka 13】

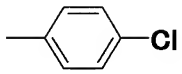
Q1a = 

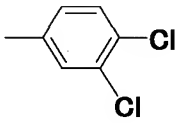
Q1b = 

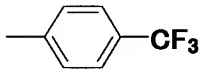
Q1c = 

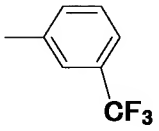
Q1d = 

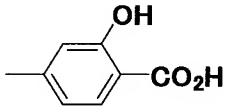
Q1e = 

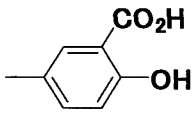
Q1f = 

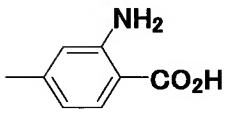
Q1g = 

Q1h = 

Q1i = 

A3g = 

A3h = 

A3i = 

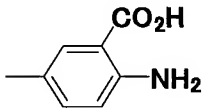
A3i = 

Table 4

No	R^{12}	R^{13}	R^{14}	R^{15}
1	Q1a	Me	H	A3g
2	Q1a	Me	H	A3h
3	Q1a	Me	H	A3i
4	Q1a	Me	H	A3j
5	Q1a	Me	Me	A3g
6	Q1a	Me	Me	A3h
7	Q1a	Me	Me	A3i
8	Q1a	Me	Me	A3j
9	Q1a	CF3	H	A3g
10	Q1a	CF3	H	A3h
11	Q1a	CF3	H	A3i
12	Q1a	CF3	H	A3j
13	Q1a	CF3	Me	A3g
14	Q1a	CF3	Me	A3h
15	Q1a	CF3	Me	A3i
16	Q1a	CF3	Me	A3j
17	Q1b	Me	H	A3g
18	Q1b	Me	H	A3h
19	Q1b	Me	H	A3i
20	Q1b	Me	H	A3j
21	Q1b	Me	Me	A3g
22	Q1b	Me	Me	A3h
23	Q1b	Me	Me	A3i
24	Q1b	Me	Me	A3j
25	Q1b	CF3	H	A3g
26	Q1b	CF3	H	A3h
27	Q1b	CF3	H	A3i
28	Q1b	CF3	H	A3j
29	Q1b	CF3	Me	A3g
30	Q1b	CF3	Me	A3h
31	Q1b	CF3	Me	A3i
32	Q1b	CF3	Me	A3j
33	Q1c	Me	H	A3g
34	Q1c	Me	H	A3h
35	Q1c	Me	H	A3i
36	Q1c	Me	H	A3j
37	Q1c	Me	Me	A3g
38	Q1c	Me	Me	A3h
39	Q1c	Me	Me	A3i
40	Q1c	Me	Me	A3j
41	Q1c	CF3	H	A3g
42	Q1c	CF3	H	A3h
43	Q1c	CF3	H	A3i

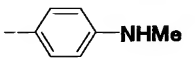
44	Q1c	CF3	H	A3j
45	Q1c	CF3	Me	A3g
46	Q1c	CF3	Me	A3h
47	Q1c	CF3	Me	A3i
48	Q1c	CF3	Me	A3j
49	Q1d	Me	H	A3g
50	Q1d	Me	H	A3h
51	Q1d	Me	H	A3i
52	Q1d	Me	H	A3j
53	Q1d	Me	Me	A3g
54	Q1d	Me	Me	A3h
55	Q1d	Me	Me	A3i
56	Q1d	Me	Me	A3j
57	Q1d	CF3	H	A3g
58	Q1d	CF3	H	A3h
59	Q1d	CF3	H	A3i
60	Q1d	CF3	H	A3j
61	Q1d	CF3	Me	A3g
62	Q1d	CF3	Me	A3h
63	Q1d	CF3	Me	A3i
64	Q1d	CF3	Me	A3j
65	Q1e	Me	H	A3g
66	Q1e	Me	H	A3h
67	Q1e	Me	H	A3i
68	Q1e	Me	H	A3j
69	Q1e	Me	Me	A3g
70	Q1e	Me	Me	A3h
71	Q1e	Me	Me	A3i
72	Q1e	Me	Me	A3j
73	Q1e	CF3	H	A3g
74	Q1e	CF3	H	A3h
75	Q1e	CF3	H	A3i
76	Q1e	CF3	H	A3j
77	Q1e	CF3	Me	A3g
78	Q1e	CF3	Me	A3h
79	Q1e	CF3	Me	A3i
80	Q1e	CF3	Me	A3j
81	Q1f	Me	H	A3g
82	Q1f	Me	H	A3h
83	Q1f	Me	H	A3i
84	Q1f	Me	H	A3j
85	Q1f	Me	Me	A3g
86	Q1f	Me	Me	A3h
87	Q1f	Me	Me	A3i
88	Q1f	Me	Me	A3j

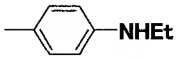
89	Q1f	CF3	H	A3g
90	Q1f	CF3	H	A3h
91	Q1f	CF3	H	A3i
92	Q1f	CF3	H	A3j
93	Q1f	CF3	Me	A3g
94	Q1f	CF3	Me	A3h
95	Q1f	CF3	Me	A3i
96	Q1f	CF3	Me	A3j
97	Q1g	Me	H	A3g
98	Q1g	Me	H	A3h
99	Q1g	Me	H	A3i
100	Q1g	Me	H	A3j
101	Q1g	Me	Me	A3g
102	Q1g	Me	Me	A3h
103	Q1g	Me	Me	A3i
104	Q1g	Me	Me	A3j
105	Q1g	CF3	H	A3g
106	Q1g	CF3	H	A3h
107	Q1g	CF3	H	A3i
108	Q1g	CF3	H	A3j
109	Q1g	CF3	Me	A3g
110	Q1g	CF3	Me	A3h
111	Q1g	CF3	Me	A3i
112	Q1g	CF3	Me	A3j
113	Q1h	Me	H	A3g
114	Q1h	Me	H	A3h
115	Q1h	Me	H	A3i
116	Q1h	Me	H	A3j
117	Q1h	Me	Me	A3g
118	Q1h	Me	Me	A3h
119	Q1h	Me	Me	A3i
120	Q1h	Me	Me	A3j
121	Q1h	CF3	H	A3g
122	Q1h	CF3	H	A3h
123	Q1h	CF3	H	A3i
124	Q1h	CF3	H	A3j
125	Q1h	CF3	Me	A3g
126	Q1h	CF3	Me	A3h
127	Q1h	CF3	Me	A3i
128	Q1h	CF3	Me	A3j
129	Q1i	Me	H	A3g
130	Q1i	Me	H	A3h
131	Q1i	Me	H	A3i
132	Q1i	Me	H	A3j
133	Q1i	Me	Me	A3g

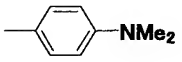
134	Q1i	Me	Me	A3h
135	Q1i	Me	Me	A3i
136	Q1i	Me	Me	A3j
137	Q1i	CF3	H	A3g
138	Q1i	CF3	H	A3h
139	Q1i	CF3	H	A3i
140	Q1i	CF3	H	A3j
141	Q1i	CF3	Me	A3g
142	Q1i	CF3	Me	A3h
143	Q1i	CF3	Me	A3i
144	Q1i	CF3	Me	A3j

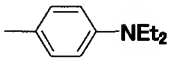
134) The compounds wherein R^7, R^8, R^9 and R^{10} are any of the following combinations in Table 5, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof. The symbols in Table 5 denote the following substituents.

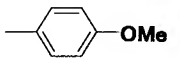
【Ka 14】

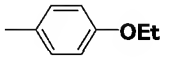
A1a = 

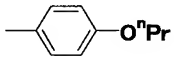
A1b = 

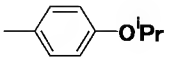
A1c = 

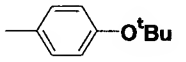
A1d = 

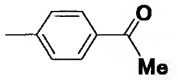
A1e = 

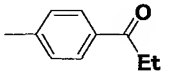
A1f = 

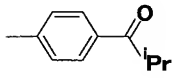
A1g = 

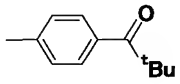
A1h = 

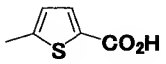
A1i = 

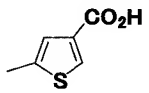
A1j = 

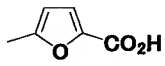
A1k = 

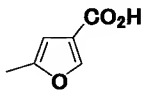
A1l= 

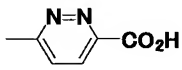
A1m= 

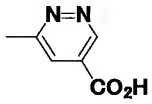
Q3a = 

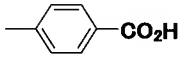
Q3b = 

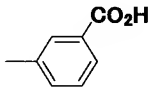
Q3c = 

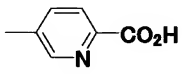
Q3d = 

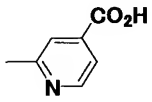
Q3e = 

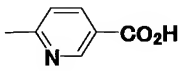
Q3f= 

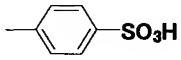
Q3g= 

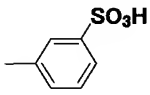
Q3h= 

Q3i= 

Q3j= 

Q3k= 

Q3l = 

Q3m = 

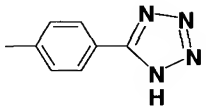
Q3n= 

Table 5

	R^7	R^8	R^9	R^{10}
1	A1a	Me	H	Q3a
2	A1a	Me	H	Q3b
3	A1a	Me	H	Q3c
4	A1a	Me	H	Q3d
5	A1a	Me	H	Q3e
6	A1a	Me	H	Q3f
7	A1a	Me	H	Q3g
8	A1a	Me	H	Q3h
9	A1a	Me	H	Q3i
10	A1a	Me	H	Q3j
11	A1a	Me	H	Q3k
12	A1a	Me	H	Q3l
13	A1a	Me	H	Q3m
14	A1a	Me	H	Q3n
15	A1a	Me	Me	Q3a
16	A1a	Me	Me	Q3b
17	A1a	Me	Me	Q3c
18	A1a	Me	Me	Q3d
19	A1a	Me	Me	Q3e
20	A1a	Me	Me	Q3f
21	A1a	Me	Me	Q3g
22	A1a	Me	Me	Q3h
23	A1a	Me	Me	Q3i
24	A1a	Me	Me	Q3j
25	A1a	Me	Me	Q3k
26	A1a	Me	Me	Q3l
27	A1a	Me	Me	Q3m
28	A1a	Me	Me	Q3n
29	A1b	Me	H	Q3a
30	A1b	Me	H	Q3b
31	A1b	Me	H	Q3c
32	A1b	Me	H	Q3d
33	A1b	Me	H	Q3e
34	A1b	Me	H	Q3f
35	A1b	Me	H	Q3g
36	A1b	Me	H	Q3h
37	A1b	Me	H	Q3i
38	A1b	Me	H	Q3j
39	A1b	Me	H	Q3k
40	A1b	Me	H	Q3l
41	A1b	Me	H	Q3m
42	A1b	Me	H	Q3n
43	A1b	Me	Me	Q3a

44	A1b	Me	Me	Q3b
45	A1b	Me	Me	Q3c
46	A1b	Me	Me	Q3d
47	A1b	Me	Me	Q3e
48	A1b	Me	Me	Q3f
49	A1b	Me	Me	Q3g
50	A1b	Me	Me	Q3h
51	A1b	Me	Me	Q3i
52	A1b	Me	Me	Q3j
53	A1b	Me	Me	Q3k
54	A1b	Me	Me	Q3l
55	A1b	Me	Me	Q3m
56	A1b	Me	Me	Q3n
57	A1c	Me	H	Q3a
58	A1c	Me	H	Q3b
59	A1c	Me	H	Q3c
60	A1c	Me	H	Q3d
61	A1c	Me	H	Q3e
62	A1c	Me	H	Q3f
63	A1c	Me	H	Q3g
64	A1c	Me	H	Q3h
65	A1c	Me	H	Q3i
66	A1c	Me	H	Q3j
67	A1c	Me	H	Q3k
68	A1c	Me	H	Q3l
69	A1c	Me	H	Q3m
70	A1c	Me	H	Q3n
71	A1c	Me	Me	Q3a
72	A1c	Me	Me	Q3b
73	A1c	Me	Me	Q3c
74	A1c	Me	Me	Q3d
75	A1c	Me	Me	Q3e
76	A1c	Me	Me	Q3f
77	A1c	Me	Me	Q3g
78	A1c	Me	Me	Q3h
79	A1c	Me	Me	Q3i
80	A1c	Me	Me	Q3j
81	A1c	Me	Me	Q3k
82	A1c	Me	Me	Q3l
83	A1c	Me	Me	Q3m
84	A1c	Me	Me	Q3n
85	A1d	Me	H	Q3a
86	A1d	Me	H	Q3b
87	A1d	Me	H	Q3c
88	A1d	Me	H	Q3d

89	A1d	Me	H	Q3e
90	A1d	Me	H	Q3f
91	A1d	Me	H	Q3g
92	A1d	Me	H	Q3h
93	A1d	Me	H	Q3i
94	A1d	Me	H	Q3j
95	A1d	Me	H	Q3k
96	A1d	Me	H	Q3l
97	A1d	Me	H	Q3m
98	A1d	Me	H	Q3n
99	A1d	Me	Me	Q3a
100	A1d	Me	Me	Q3b
101	A1d	Me	Me	Q3c
102	A1d	Me	Me	Q3d
103	A1d	Me	Me	Q3e
104	A1d	Me	Me	Q3f
105	A1d	Me	Me	Q3g
106	A1d	Me	Me	Q3h
107	A1d	Me	Me	Q3i
108	A1d	Me	Me	Q3j
109	A1d	Me	Me	Q3k
110	A1d	Me	Me	Q3l
111	A1d	Me	Me	Q3m
112	A1d	Me	Me	Q3n
113	A1e	Me	H	Q3a
114	A1e	Me	H	Q3b
115	A1e	Me	H	Q3c
116	A1e	Me	H	Q3d
117	A1e	Me	H	Q3e
118	A1e	Me	H	Q3f
119	A1e	Me	H	Q3g
120	A1e	Me	H	Q3h
121	A1e	Me	H	Q3i
122	A1e	Me	H	Q3j
123	A1e	Me	H	Q3k
124	A1e	Me	H	Q3l
125	A1e	Me	H	Q3m
126	A1e	Me	H	Q3n
127	A1e	Me	Me	Q3a
128	A1e	Me	Me	Q3b
129	A1e	Me	Me	Q3c
130	A1e	Me	Me	Q3d
131	A1e	Me	Me	Q3e
132	A1e	Me	Me	Q3f
133	A1e	Me	Me	Q3g

134	A1e	Me	Me	Q3h
135	A1e	Me	Me	Q3i
136	A1e	Me	Me	Q3j
137	A1e	Me	Me	Q3k
138	A1e	Me	Me	Q3l
139	A1e	Me	Me	Q3m
140	A1e	Me	Me	Q3n
141	A1f	Me	H	Q3a
142	A1f	Me	H	Q3b
143	A1f	Me	H	Q3c
144	A1f	Me	H	Q3d
145	A1f	Me	H	Q3e
146	A1f	Me	H	Q3f
147	A1f	Me	H	Q3g
148	A1f	Me	H	Q3h
149	A1f	Me	H	Q3i
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151	A1f	Me	H	Q3k
152	A1f	Me	H	Q3l
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154	A1f	Me	H	Q3n
155	A1f	Me	Me	Q3a
156	A1f	Me	Me	Q3b
157	A1f	Me	Me	Q3c
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160	A1f	Me	Me	Q3f
161	A1f	Me	Me	Q3g
162	A1f	Me	Me	Q3h
163	A1f	Me	Me	Q3i
164	A1f	Me	Me	Q3j
165	A1f	Me	Me	Q3k
166	A1f	Me	Me	Q3l
167	A1f	Me	Me	Q3m
168	A1f	Me	Me	Q3n
169	A1g	Me	H	Q3a
170	A1g	Me	H	Q3b
171	A1g	Me	H	Q3c
172	A1g	Me	H	Q3d
173	A1g	Me	H	Q3e
174	A1g	Me	H	Q3f
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176	A1g	Me	H	Q3h
177	A1g	Me	H	Q3i
178	A1g	Me	H	Q3j

179	A1g	Me	H	Q3k
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184	A1g	Me	Me	Q3b
185	A1g	Me	Me	Q3c
186	A1g	Me	Me	Q3d
187	A1g	Me	Me	Q3e
188	A1g	Me	Me	Q3f
189	A1g	Me	Me	Q3g
190	A1g	Me	Me	Q3h
191	A1g	Me	Me	Q3i
192	A1g	Me	Me	Q3j
193	A1g	Me	Me	Q3k
194	A1g	Me	Me	Q3l
195	A1g	Me	Me	Q3m
196	A1g	Me	Me	Q3n
197	A1h	Me	H	Q3a
198	A1h	Me	H	Q3b
199	A1h	Me	H	Q3c
200	A1h	Me	H	Q3d
201	A1h	Me	H	Q3e
202	A1h	Me	H	Q3f
203	A1h	Me	H	Q3g
204	A1h	Me	H	Q3h
205	A1h	Me	H	Q3i
206	A1h	Me	H	Q3j
207	A1h	Me	H	Q3k
208	A1h	Me	H	Q3l
209	A1h	Me	H	Q3m
210	A1h	Me	H	Q3n
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212	A1h	Me	Me	Q3b
213	A1h	Me	Me	Q3c
214	A1h	Me	Me	Q3d
215	A1h	Me	Me	Q3e
216	A1h	Me	Me	Q3f
217	A1h	Me	Me	Q3g
218	A1h	Me	Me	Q3h
219	A1h	Me	Me	Q3i
220	A1h	Me	Me	Q3j
221	A1h	Me	Me	Q3k
222	A1h	Me	Me	Q3l
223	A1h	Me	Me	Q3m

224	A1h	Me	Me	Q3n
225	A1i	Me	H	Q3a
226	A1i	Me	H	Q3b
227	A1i	Me	H	Q3c
228	A1i	Me	H	Q3d
229	A1i	Me	H	Q3e
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231	A1i	Me	H	Q3g
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234	A1i	Me	H	Q3j
235	A1i	Me	H	Q3k
236	A1i	Me	H	Q3l
237	A1i	Me	H	Q3m
238	A1i	Me	H	Q3n
239	A1i	Me	Me	Q3a
240	A1i	Me	Me	Q3b
241	A1i	Me	Me	Q3c
242	A1i	Me	Me	Q3d
243	A1i	Me	Me	Q3e
244	A1i	Me	Me	Q3f
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247	A1i	Me	Me	Q3i
248	A1i	Me	Me	Q3j
249	A1i	Me	Me	Q3k
250	A1i	Me	Me	Q3l
251	A1i	Me	Me	Q3m
252	A1i	Me	Me	Q3n
253	A1j	Me	H	Q3a
254	A1j	Me	H	Q3b
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256	A1j	Me	H	Q3d
257	A1j	Me	H	Q3e
258	A1j	Me	H	Q3f
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260	A1j	Me	H	Q3h
261	A1j	Me	H	Q3i
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265	A1j	Me	H	Q3m
266	A1j	Me	H	Q3n
267	A1j	Me	Me	Q3a
268	A1j	Me	Me	Q3b

269	A1j	Me	Me	Q3c
270	A1j	Me	Me	Q3d
271	A1j	Me	Me	Q3e
272	A1j	Me	Me	Q3f
273	A1j	Me	Me	Q3g
274	A1j	Me	Me	Q3h
275	A1j	Me	Me	Q3i
276	A1j	Me	Me	Q3j
277	A1j	Me	Me	Q3k
278	A1j	Me	Me	Q3l
279	A1j	Me	Me	Q3m
280	A1j	Me	Me	Q3n
281	A1k	Me	H	Q3a
282	A1k	Me	H	Q3b
283	A1k	Me	H	Q3c
284	A1k	Me	H	Q3d
285	A1k	Me	H	Q3e
286	A1k	Me	H	Q3f
287	A1k	Me	H	Q3g
288	A1k	Me	H	Q3h
289	A1k	Me	H	Q3i
290	A1k	Me	H	Q3j
291	A1k	Me	H	Q3k
292	A1k	Me	H	Q3l
293	A1k	Me	H	Q3m
294	A1k	Me	H	Q3n
295	A1k	Me	Me	Q3a
296	A1k	Me	Me	Q3b
297	A1k	Me	Me	Q3c
298	A1k	Me	Me	Q3d
299	A1k	Me	Me	Q3e
300	A1k	Me	Me	Q3f
301	A1k	Me	Me	Q3g
302	A1k	Me	Me	Q3h
303	A1k	Me	Me	Q3i
304	A1k	Me	Me	Q3j
305	A1k	Me	Me	Q3k
306	A1k	Me	Me	Q3l
307	A1k	Me	Me	Q3m
308	A1k	Me	Me	Q3n
309	A1l	Me	H	Q3a
310	A1l	Me	H	Q3b
311	A1l	Me	H	Q3c
312	A1l	Me	H	Q3d
313	A1l	Me	H	Q3e

314	A1l	Me	H	Q3f
315	A1l	Me	H	Q3g
316	A1l	Me	H	Q3h
317	A1l	Me	H	Q3i
318	A1l	Me	H	Q3j
319	A1l	Me	H	Q3k
320	A1l	Me	H	Q3l
321	A1l	Me	H	Q3m
322	A1l	Me	H	Q3n
323	A1l	Me	Me	Q3a
324	A1l	Me	Me	Q3b
325	A1l	Me	Me	Q3c
326	A1l	Me	Me	Q3d
327	A1l	Me	Me	Q3e
328	A1l	Me	Me	Q3f
329	A1l	Me	Me	Q3g
330	A1l	Me	Me	Q3h
331	A1l	Me	Me	Q3i
332	A1l	Me	Me	Q3j
333	A1l	Me	Me	Q3k
334	A1l	Me	Me	Q3l
335	A1l	Me	Me	Q3m
336	A1l	Me	Me	Q3n
337	A1m	Me	H	Q3a
338	A1m	Me	H	Q3b
339	A1m	Me	H	Q3c
340	A1m	Me	H	Q3d
341	A1m	Me	H	Q3e
342	A1m	Me	H	Q3f
343	A1m	Me	H	Q3g
344	A1m	Me	H	Q3h
345	A1m	Me	H	Q3i
346	A1m	Me	H	Q3j
347	A1m	Me	H	Q3k
348	A1m	Me	H	Q3l
349	A1m	Me	H	Q3m
350	A1m	Me	H	Q3n
351	A1m	Me	Me	Q3a
352	A1m	Me	Me	Q3b
353	A1m	Me	Me	Q3c
354	A1m	Me	Me	Q3d
355	A1m	Me	Me	Q3e
356	A1m	Me	Me	Q3f
357	A1m	Me	Me	Q3g
358	A1m	Me	Me	Q3h

359	A1m	Me	Me	Q3i
360	A1m	Me	Me	Q3j
361	A1m	Me	Me	Q3k
362	A1m	Me	Me	Q3l
363	A1m	Me	Me	Q3m
364	A1m	Me	Me	Q3n

135) The thrombopoietin receptor activators represented by 1).

136) The thrombopoietin receptor activators represented by 2).

137) The thrombopoietin receptor activators represented by 3).

138) The thrombopoietin receptor activators represented by 4).

139) The thrombopoietin receptor activators represented by 5).

140) The thrombopoietin receptor activators represented by 6).

141) The thrombopoietin receptor activators represented by 7).

142) The thrombopoietin receptor activators represented by 8).

143) The thrombopoietin receptor activators represented by 9).

144) The thrombopoietin receptor activators represented by 10).

145) The thrombopoietin receptor activators represented by 11).

146) The thrombopoietin receptor activators represented by 12).

147) The thrombopoietin receptor activators represented by 13).

148) The thrombopoietin receptor activators represented

by 14).

149) The thrombopoietin receptor activators represented by 15).

150) The thrombopoietin receptor activators represented by 16).

151) The thrombopoietin receptor activators represented by 17).

152) The thrombopoietin receptor activators represented by 18).

153) The thrombopoietin receptor activators represented by 19).

154) The thrombopoietin receptor activators represented by 20).

155) The thrombopoietin receptor activators represented by 21).

156) The thrombopoietin receptor activators represented by 22).

157) The thrombopoietin receptor activators represented by 23).

158) The thrombopoietin receptor activators represented by 24).

159) The thrombopoietin receptor activators represented by 25).

160) The thrombopoietin receptor activators represented by 26).

161) The thrombopoietin receptor activators represented by 27).

162) The thrombopoietin receptor activators represented by 28).

163) The thrombopoietin receptor activators represented by 29).

164) The thrombopoietin receptor activators represented by 30).

165) The thrombopoietin receptor activators represented by 31).

166) The thrombopoietin receptor activators represented by 32).

167) The thrombopoietin receptor activators represented by 33).

168) The thrombopoietin receptor activators represented by 34).

169) The thrombopoietin receptor activators represented by 35).

170) The thrombopoietin receptor activators represented by 36).

171) The thrombopoietin receptor activators represented by 37).

172) The thrombopoietin receptor activators represented by 38).

173) The thrombopoietin receptor activators represented by 39).

174) The thrombopoietin receptor activators represented by 40).

175) The thrombopoietin receptor activators represented

by 41).

176) The thrombopoietin receptor activators represented by 42).

177) The thrombopoietin receptor activators represented by 43).

178) The thrombopoietin receptor activators represented by 44).

179) The thrombopoietin receptor activators represented by 45).

180) The thrombopoietin receptor activators represented by 46).

181) The thrombopoietin receptor activators represented by 47).

182) The thrombopoietin receptor activators represented by 48).

183) The thrombopoietin receptor activators represented by 49).

184) The thrombopoietin receptor activators represented by 50).

185) The thrombopoietin receptor activators represented by 51).

186) The thrombopoietin receptor activators represented by 52).

187) The thrombopoietin receptor activators represented by 53).

188) The thrombopoietin receptor activators represented by 54).

189) The thrombopoietin receptor activators represented by 55).

190) The thrombopoietin receptor activators represented by 56).

191) The thrombopoietin receptor activators represented by 57).

192) The thrombopoietin receptor activators represented by 58).

193) The thrombopoietin receptor activators represented by 59).

194) The thrombopoietin receptor activators represented by 60).

195) The thrombopoietin receptor activators represented by 61).

196) The thrombopoietin receptor activators represented by 62).

197) The thrombopoietin receptor activators represented by 63).

198) The thrombopoietin receptor activators represented by 64).

199) The thrombopoietin receptor activators represented by 65).

200) The thrombopoietin receptor activators represented by 66).

201) The thrombopoietin receptor activators represented by 67).

202) The thrombopoietin receptor activators represented

by 68).

203) The thrombopoietin receptor activators represented by 69).

204) The thrombopoietin receptor activators represented by 70).

205) The thrombopoietin receptor activators represented by 71).

206) The thrombopoietin receptor activators represented by 72).

207) The thrombopoietin receptor activators represented by 73).

208) The thrombopoietin receptor activators represented by 74).

209) The thrombopoietin receptor activators represented by 75).

210) The thrombopoietin receptor activators represented by 76).

211) The thrombopoietin receptor activators represented by 77).

212) The thrombopoietin receptor activators represented by 78).

213) The thrombopoietin receptor activators represented by 79).

214) The thrombopoietin receptor activators represented by 80).

215) The thrombopoietin receptor activators represented by 81).

216) The thrombopoietin receptor activators represented by 82).

217) The thrombopoietin receptor activators represented by 83).

218) The thrombopoietin receptor activators represented by 84).

219) The thrombopoietin receptor activators represented by 85).

220) The thrombopoietin receptor activators represented by 86).

221) The thrombopoietin receptor activators represented by 87).

222) The thrombopoietin receptor activators represented by 88).

223) The thrombopoietin receptor activators represented by 89).

224) The thrombopoietin receptor activators represented by 90).

225) The thrombopoietin receptor activators represented by 91).

226) The thrombopoietin receptor activators represented by 92).

227) The thrombopoietin receptor activators represented by 93).

228) The thrombopoietin receptor activators represented by 94).

229) The thrombopoietin receptor activators represented

by 95).

230) The thrombopoietin receptor activators represented by 96).

231) The thrombopoietin receptor activators represented by 97).

232) The thrombopoietin receptor activators represented by 98).

233) The thrombopoietin receptor activators represented by 99).

234) The thrombopoietin receptor activators represented by 100).

235) The thrombopoietin receptor activators represented by 101).

236) The thrombopoietin receptor activators represented by 102).

237) The thrombopoietin receptor activators represented by 103).

238) The thrombopoietin receptor activators represented by 104).

239) The thrombopoietin receptor activators represented by 105).

240) The thrombopoietin receptor activators represented by 106).

241) The thrombopoietin receptor activators represented by 107).

242) The thrombopoietin receptor activators represented by 108).

243) The thrombopoietin receptor activators represented by 109).

244) The thrombopoietin receptor activators represented by 110).

245) The thrombopoietin receptor activators represented by 111).

246) The thrombopoietin receptor activators represented by 112).

247) The thrombopoietin receptor activators represented by 113).

248) The thrombopoietin receptor activators represented by 114).

249) The thrombopoietin receptor activators represented by 115).

250) The thrombopoietin receptor activators represented by 116).

251) The thrombopoietin receptor activators represented by 117).

252) The thrombopoietin receptor activators represented by 118).

253) The thrombopoietin receptor activators represented by 119).

254) The thrombopoietin receptor activators represented by 120).

255) The thrombopoietin receptor activators represented by 121).

256) The thrombopoietin receptor activators represented

by 122).

257) The thrombopoietin receptor activators represented by 123).

258) The thrombopoietin receptor activators represented by 124).

259) The thrombopoietin receptor activators represented by 125).

260) The thrombopoietin receptor activators represented by 126).

261) The thrombopoietin receptor activators represented by 127).

262) The thrombopoietin receptor activators represented by 128).

263) The thrombopoietin receptor activators represented by 129).

264) The thrombopoietin receptor activators represented by 130).

265) The thrombopoietin receptor activators represented by 131).

266) The thrombopoietin receptor activators represented by 132).

267) The thrombopoietin receptor activators represented by 133).

268) The thrombopoietin receptor activators represented by 134).

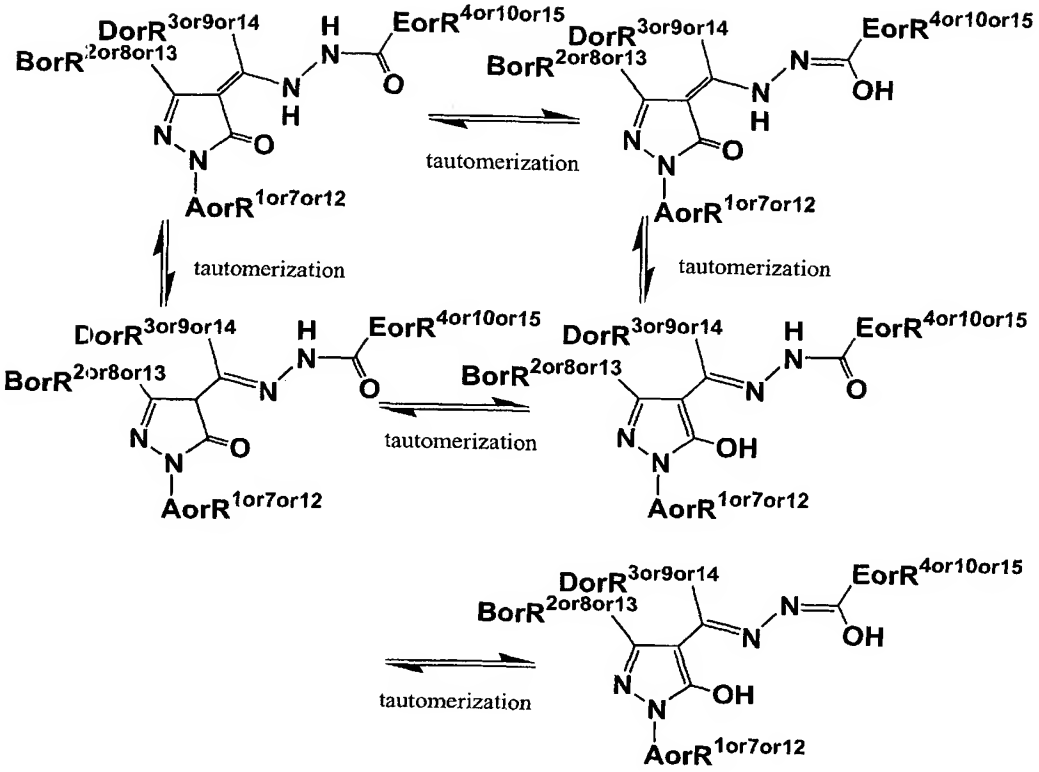
269) Preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin

receptor is effective which contain the thrombopoietin receptor activators represented by any of 135) to 268) or the formula (1), the formula (2), the formula (3) or the formula (4), tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

270) Platelet increasing agents containing the thrombopoietin receptor activators represented by any of 135) to 268) or the formula (1), the formula (2), the formula (3) or the formula (4), tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

The compounds of the present invention represented by the formula (1), the formula (2), the formula (3) or the formula (4) may be present in the form of pyrazoles which undergo the following tautomerizations, mixtures or mixtures of isomers thereof. When the compounds of the present invention have optical isomers, diastereomers or geometric isomers, the compounds of the present invention may be in the form of mixtures thereof or in the resolved form.

【Ka 15】



The compounds of the present invention represented by the formula (1), the formula (2), the formula (3) or the formula (4) or pharmaceutically acceptable salts thereof may be in the form of arbitrary crystals or arbitrary hydrates. The present invention covers these crystals, hydrates and mixtures. They may be in the form of optional solvates with organic solvents such as acetone, ethanol and tetrahydrofuran, and the present invention covers any of these forms.

The compounds of the present invention represented by the formula (1), the formula (2), the formula (3) or the formula (4) may be converted to pharmaceutically

acceptable salts or may be liberated from the resulting salts, if necessary. The pharmaceutically acceptable salts of the present invention may be, for example, salts with alkali metals (such as lithium, sodium and potassium), alkaline earth metals (such as magnesium and calcium), ammonium, organic bases and amino acids. They may be salts with inorganic acids (such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid) and organic acids (such as acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid and p-toluenesulfonic acid). They may also be complexes with transition metals (such as copper and zinc).

The compounds which serve as prodrugs are derivatives of the present invention having chemically or metabolically degradable groups which give pharmacologically active compounds of the present invention upon solvolysis or under physiological conditions in vivo. Methods for selecting or producing appropriate prodrugs are disclosed, for example, in Design of Prodrug (Elsevier, Amsterdam 1985). In the present invention, when the compound has a hydroxyl group, acyloxy derivatives obtained by reacting the compound with appropriate acyl halides or appropriate acid anhydrides may, for example, be mentioned as a prodrug. Acyloxys particularly preferred as prodrugs include $-OCOC_2H_5$, -OCO(t-Bu), $-OCOC_{15}H_{31}$, -OCO(m-CO_2Na-Ph), $-OCOCH_2CH_2CO_2Na$, $-OCOCH(NH_2)CH_3$, $-OCOCH_2N(CH_3)_2$ and the

like. When the compound of the present invention has an amino group, amide derivatives obtained by reacting the compound having an amino group with appropriate acid halides or appropriate mixed acid anhydrides may, for example, be mentioned as prodrugs. Amides particularly preferred as prodrugs include $-NHCO(CH_2)_{20}OCH_3$, $-NHCOCH(NH_2)CH_3$ and the like. When the compound of the present invention has a carboxyl group, carboxylic acid esters with aliphatic alcohols or carboxylic acid esters obtained by the reaction of an alcoholic free hydroxyl group of 1,2- or 1,3-digylcerides may, for example, be mentioned as prodrugs. Particularly preferred prodrugs are methyl esters and ethyl esters.

The preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective or platelet increasing agents which contain the thrombopoietin receptor activators, tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof as an active ingredient may usually be administered as oral medicines such as tablets, capsules, powder, granules, pills and syrup, as rectal medicines, percutaneous medicines or injections. The agents of the present invention may be administered as a single therapeutic agent or as a mixture with other therapeutic agents. Though they may be administered as they are, they are usually administered in the form of medical compositions. These pharmaceutical preparations

can be obtained by adding pharmacologically and pharmaceutically acceptable additives by conventional methods. Namely, for oral medicines, ordinary excipients, lubricants, binders, disintegrants, humectants, plasticizers and coating agents may be used. Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs or may be supplied as dry syrups to be mixed with water or other appropriate solvents before use. Such liquid preparations may contain ordinary additives such as suspending agents, perfumes, diluents and emulsifiers. In the case of rectal administration, they may be administered as suppositories. Suppositories may use an appropriate substance such as cacao butter, laurin tallow, Macrogol, glycerogelatin, Witepsol, sodium stearate and mixtures thereof as the base and may contain an emulsifier, a suspending agent, a preservative and the like. For injections, a solvent or a solubilizing agent such as distilled water for injection, physiological saline, 5% glucose solution and propylene glycol and pharmaceutical components such as a pH regulator, an isotonizing agent and a stabilizer may be used to form aqueous dosage forms or dosage forms which need dissolution before use.

The dose of the agents of the present invention for administration to human is usually about from 0.1 to 1000 mg/human/day in the case of oral drugs or rectal

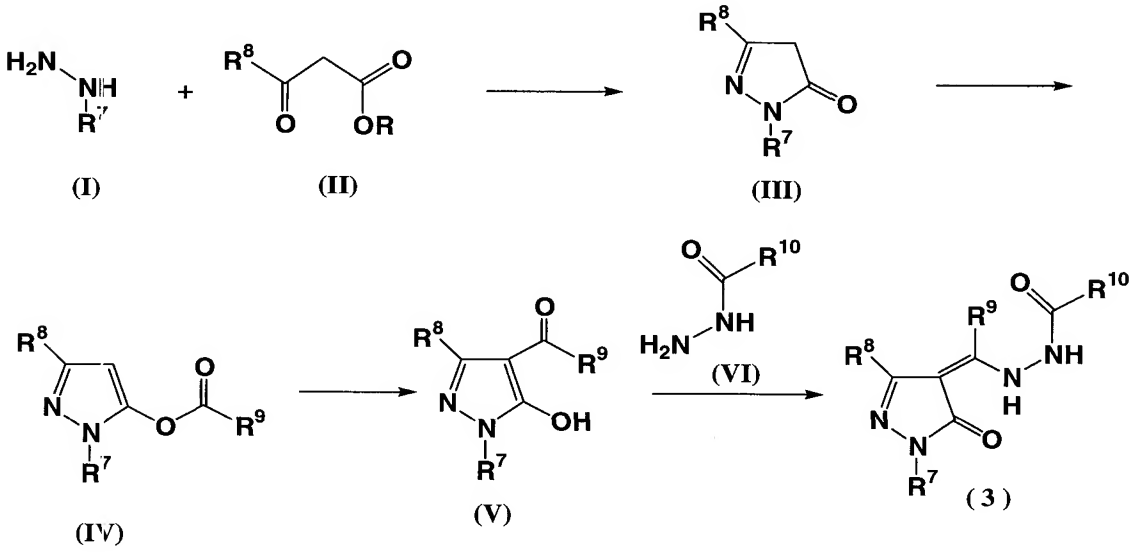
administration and about from 0.05 mg to 500 mg/human/day in the case of injections, though it depends on the age and conditions of the patient. The above-mentioned ranges are mere examples, and the dose should be determined from the conditions of the patient.

The present invention is used when the use of compounds which have thrombopoietin receptor affinity and act as thrombopoietin receptor agonists are expected to improve pathological conditions. For example, hematological disorders accompanied by abnormal platelet count may be mentioned. Specifically, it is effective for therapy or prevention of human and mammalian diseases caused by abnormal megakaryopoiesis, especially those accompanied by thrombocytopenia. Examples of such diseases include thrombocytopenia accompanying chemotherapy or radiotherapy of cancer, thrombocytopenia caused by bone marrow transplantation, surgery and serious infection, or gastrointestinal bleeding, but such diseases are not restricted to these mentioned. Typical thrombocytopenias such as aplastic anemia, idiopathic thrombocytopenic purpura, myelodysplastic syndrome and thrombopoietin deficiency are also targets of the agents of the present invention. The present invention may be used as a peripheral stem cell mobilizer, a megakaryocytic leukemia cell differentiation inducer and a platelet increasing agent for platelet donors. In addition, potential applications include therapeutic

angiogenesis based on differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells, prevention and therapy of arteriosclerosis, myocardial infarction, unstable angina, peripheral artery occlusive disease, but there is no restriction.

The pyrazolone compounds represented by the formula (1), the formula (2), the formula (3) or the formula (4) are prepared by the process illustrated below in reference to the pyrazolone compounds represented by the formula (3).

【Ka 16】



The pyrazolones (III) are obtained by known methods (Syn. Comm., 20(20), 3213 (1990), Chem. Ber., 59, 320 (1926), Monatsh. Chem., 89, 30 (1958)), for example, by reacting β-keto esters (II) with hydrazines (R^7NHNH_2 or salts thereof) in acetic acid with reflux. Acylation of them with acyl halides (R^9COCl) or acid anhydrides

$((R^9CO)_2O)$ to (IV) followed by Fries rearrangement in the presence of potassium carbonate in dioxane with heating gives 4-acyl-5-hydroxypyrazoles (V). 4-Formyl-5-hydroxypyrazole (V) (R^9 = H) are obtainable by reacting the pyrazolones (III) with $POCl_3$-DMF. They are heated with hydrazides ($R^{10}CONHNH_2$ (VI) or salts thereof) optionally in the presence of a catalyst in a solvent to give the desired products. Syntheses of hydrazides (VI) are disclosed in the following documents.

1) Synthetic Commun., 28, (7) pp.1223-1231 (1998)
2) J. Chem. Soc., 1225 (1948)
3) J. Chem. Soc., 2831 (1952)
4) WO03/7328
5) Nihon Kagaku Zasshi, 88(5), p.73 (1967)
6) Journal of Heterocyclic Chemistry, 28(17), 17 (1991)

The compounds of the present invention are usually obtained with high purity by recrystallization or washing with solvents because most of them have good crystallizability. However, if necessary, they may be purified by column chromatography, thin layer chromatography, high performance liquid chromatography (HPLC) or high performance liquid chromatography-mass spectrometry (LC-MS).

【Examples】

Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no

means restricted by these specific Examples.

In high performance liquid chromatography-mass spectrometry (LC-MS), the retention time was measured under the following conditions.

Column: Waters XTerra MSC18 4.6×50 mm

Eluent: H_2O:CH_3CN = 85:15 → 15:85

Syntheses of the compounds of Reference Synthetic Examples followed Examples 2-5 (pages 12-14) of WO01/34585.

SYNTHETIC EXAMPLE 1

Synthesis of 2,4-dihydroxybenzoic N'-(1-(3-methyl-5-oxo-1-(4-iodophenyl)-1,5-dihydro-pyrazol-4-ylidene)-ethyl)-hydrazide

1.03 g (3 mmol) of 1-(5-hydroxy-1-(4-iodophenyl)-3-methyl-1H-pyrazol-4-yl)-ethanone and 505 mg (3 mmol) of 2,4-dihydroxybenzoic hydrazide were dissolved in 50 ml of DMSO and heated at 85°C for 9 hours with stirring. After cooling and evaporation of the solvent, the crude product was recrystallized from chloroform/ether to give 1.39 g of the desired product as a pale brown solid (yield 94%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.36 (s, 3H), 2.42 (s, 3H), 2.54 (s, 3H), 6.36 (t, 1H, J = 2 Hz), 6.40 (d, 1H, J = 2 Hz), 7.68-7.76 (m, 3H), 7.86 (d, 2H, J = 9 Hz)

LC/MS

M^+ = 492.27 (2.88 min)

SYNTHETIC EXAMPLE 2

Synthesis of 3,5-dihydroxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3,5-dihydroxybenzoic hydrazide, 40.1 mg of the desired product was obtained in the same manner as in Synthetic Example 1 as a yellow solid (yield 40%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.36 (s, 3H), 2.41 (s, 3H), 6.45 (s, 1H), 6.76 (s, 2H), 7.41 (d, 2H, J = 8.8 Hz), 7.89 (d, 2H, J = 8.8 Hz), 9.65 (s, 2H), 11.08 (s, 1H).

LC/MS

M^+ = 422 (2.19 min).

SYNTHETIC EXAMPLE 3

Synthesis of 3,5-dihydroxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3,5-dihydroxybenzoic hydrazide, 57.0 mg of the desired product was obtained in the same manner as in Synthetic Example 1 as a pale red solid (yield 73%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.41 (s, 3H), 6.45 (s, 1H), 6.75 (s, 1H), 6.76(s,1H), 7.14 (d, 1H,

J = 8.3 Hz), 7.70 (dd, 1H, J = 1.9, 8.3 Hz), 7.77 (d, 1H, J = 1.9 Hz), 9.66 (s, 2H), 11.09 (s, 1H).

LC/MS

M^+ = 394 (1.82 min).

SYNTHETIC EXAMPLE 4

Synthesis of 4-methoxycarbonyl-benzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1) Synthesis of 4-methoxycarbonylbenzhydrazide

The known procedure disclosed in the literature (Synthetic Communications, 28(7), 1223-1231, (1998)) was followed using monomethyl terephthalate and tetramethylfluoroformamidinium hexafluorophosphate to give 1.36 g of a colorless solid (yield 70%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 3.86 (s, 3H), 4.56 (s, 2H), 7.93 (d, 2H, J = 8.3 Hz), 8.02 (d, 2H, J = 8.3 Hz), 9.96 (bs, 1H).

2) Synthesis of 4-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

30.5 mg (0.11 mmol) of 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 23.1 mg (0.11 mmol) of 4-methoxycarbonylbenzhydrazide were dissolved in 3.0 ml of DMF and stirred at 100°C for 3 hours. After cooling and evaporation of the solvent, the crude product was recrystallized from ethyl acetate/n-hexane to give 32.9 mg of the desired product as a yellow

solid (yield 66%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 7.41 (d, 2H, J = 8.7 Hz), 7.89 (d, 2H, J = 8.7 Hz), 8.05 (d, 2H, J = 8.4 Hz), 8.12 (d, 2H, J = 8.4 Hz).

LC/MS

M^+ = 448 (2.64 min).

SYNTHETIC EXAMPLE 5

Synthesis of 4-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

To 23.2 mg (0.05 mmol) of the 4-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 4 in 2.0 ml of methanol, 255 µl (0.255 mmol) of 1M aqueous sodium hydroxide was added at room temperature, and the mixture was heated at from 60°C to 80°C for 3.5 hours. After it was cooled to room temperature, 255 µl (0.255 mmol) of 1M hydrochloric acid was added, and the precipitated solid was collected by filtration to obtain 13.9 mg of the desired product as a pale brown solid (yield 61%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.45 (s, 3H), 7.41 (d, 2H, J = 8.7 Hz), 7.89 (d, 2H, J = 8.7 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.09 (d, 2H, J = 8.3 Hz), 11.44 (s, 1H).

LC/MS

M^+ = 434 (2.38 min).

SYNTHETIC EXAMPLE 6

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 53.0 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a pale yellow solid (yield 64%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 3.89 (s, 3H), 7.14 (d, 1H, J = 8.5 Hz), 7.71 (dd, 1H, J = 1.9, 8.5 Hz), 7.77 (d, 1H, J = 1.9 Hz), 8.05 (d, 2H, J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz).

LC/MS

M^+ = 420 (2.34 min).

SYNTHETIC EXAMPLE 7

Synthesis of 4-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 6, 21.5 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 71%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 7.14 (d, 1H, J = 8.3 Hz), 7.70 (dd, 1H, J = 1.9, 8.3 Hz), 7.77 (d, 1H, J = 1.9 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.10 (d, 2H, J = 8.3 Hz), 11.45 (s, 1H).

LC/MS

M^+ = 406 (2.03 min).

SYNTHETIC EXAMPLE 8

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(5-hydroxy-3-methyl-1-(3-trifluoromethylphenyl)-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 59.9 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield 65%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 3.91 (s, 3H), 7.49 (d, 1H, J = 7.4 Hz), 7.66 (dd, 1H, J = 8.0, 8.3 Hz), 8.06 (d, 2H, J = 8.3 Hz), 8.13 (d, 2H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.0 Hz), 8.45 (s, 1H), 11.55 (bs, 1H), 12.47 (bs, 1H).

LC/MS

M^+ = 460.41 (2.69 min).

SYNTHETIC EXAMPLE 9

Synthesis of 4-carboxybenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 8, 26.5 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 78%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.41 (s, 3H), 2.51 (s, 3H), 7.49 (d, 1H, J = 8.0 Hz), 7.66 (dd, 1H, J = 8.0 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.10 (d, 2H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.0 Hz), 8.45 (s, 1H), 11.52 (bs, 1H), 12.46 (bs, 1H).

LC/MS

M^+ = 446.38 (2.29 min).

SYNTHETIC EXAMPLE 10

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(5-hydroxy-3-methyl-1-(4-trifluoromethylphenyl)-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 58.9 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield 65%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 3.91 (s, 3H), 7.77 (d, 2H, J = 8.5 Hz), 8.06 (d, 2H, J = 8.5 Hz), 8.13 (d, 2H, J = 8.5 Hz), 8.26 (d, 2H, J = 8.5 Hz), 11.56 (bs, 1H), 12.46 (bs, 1H).

LC/MS

M^+ = 460.41 (2.62 min).

SYNTHETIC EXAMPLE 11

Synthesis of 4-carboxybenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 10, 18.6 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 68%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 7.77 (d, 2H, J = 8.7 Hz), 8.03 (d, 2H, J = 8.2 Hz), 8.10 (d, 2H, J = 8.2 Hz), 8.23 (d, 2H, J = 8.7 Hz), 11.53 (bs, 1H), 12.45 (bs, 1H).

LC/MS

M^+ = 446.38 (2.31 min).

SYNTHETIC EXAMPLE 12

Synthesis of 3-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1) Synthesis of 3-methoxycarbonylbenzhydrazide

The procedure in Synthetic Example 4 was followed using monomethyl isophthalate and tetramethylfluoroformamidinium hexafluorophosphate to give 244.6 mg of a yellow solid (yield > 99%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 3.89 (s, 3H), 4.61 (bs, 2H), 7.62 (dd, 1H, J = 8.0 Hz), 8.08 (dd, 2H, J = 1.8, 8.0 Hz), 8.42 (d, 1H, J = 1.8 Hz), 9.98 (bs, 1H).

LC/MS

M^+ = 194 (0.51 min).

2) Synthesis of 3-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3-methoxycarbonylbenzhydrazide, 64.6 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield 70%).

3) Synthesis of 3-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 3-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in 2), 11.2 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale brown solid (yield 50%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.45 (s, 3H), 7.42 (d, 2H, J = 8.8 Hz), 7.70 (dd, 1H, J = 7.8 Hz), 7.89 (d, 2H, J = 8.8 Hz), 8.16 (d, 1H, J = 6.9 Hz), 8.51 (s, 1H), 11.46 (bs, 1H).

LC/MS

M^+ = 434.49 (2.37 min).

SYNTHETIC EXAMPLE 13

Synthesis of 3-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1) Synthesis of 3-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3-methoxycarbonylbenzhydrazide, 27.4 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a pale yellow solid (yield 35%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 3.92 (s, 3H), 7.14 (d, 1H, J = 8.3 Hz), 7.70—7.77 (m, 3H), 8.20 (d, 2H, J = 8.0 Hz), 8.51 (s, 1H), 11.49 (s, 1H).

2) Synthesis of 3-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 3-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in 1), 17.2 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 68%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 7.14 (d, 1H, J = 8.5 Hz), 7.68—7.77 (m, 3H), 8.15-8.20 (m, 2H), 8.19 (d, 1H, J = 7.2 Hz), 8.50 (s, 1H).

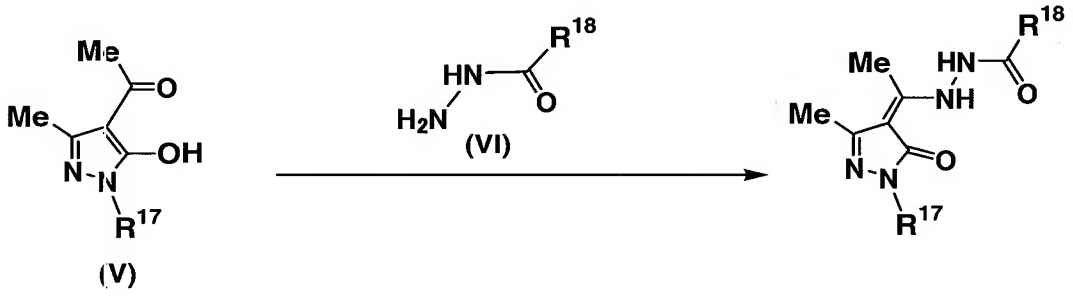
LC/MS

M^+ = 406.43 (2.03 min).

SYNTHETIC EXAMPLES 14 to 92

The structural formulae, yields, appearances, and molecular weights measured by LC/MS of the compounds synthesized by the following method based on Synthetic Example 1 are shown in Table 6.

【Ka 17】



A pyrazole derivative (V) and a benzoic hydrazide (VI) were dissolved in a solvent such as DMF, EtOH and DMSO in a molar ratio of 1:1 and heated at 80 to 100°C with stirring. The solvent was removed by evaporation, and the resulting crude product was dissolved in chloroform and recrystallized from a poor solvent or washed with chloroform to give the desired product.

Table 6

Synthetic Ex. No.	R^{17}	R^{18}	Yield	Appearance	Molecular weight
14	Ph	3-NO_2-Ph	37.6%	Yellow solid	379.38
15	4-t-Bu-Ph	3-NO_2-Ph	58.1%	Pale brown solid	435.48
16	Ph	2-OH-Ph	24.7%	Pale yellow solid	350.38
17	Ph	4-OH-Ph	65.1%	Pale pink solid	350.38
18	Ph	3-OH-2-Naphthyl	59.2%	Pale yellow solid	400.44
19	Ph	2,4-$(OH)_2$-Ph	41.1%	Pale yellow solid	366.38
20	Ph	3,4-$(OH)_2$-Ph	43.9%	Pale brown solid	366.38
21	Ph	2-NO_2-Ph	67.5%	Yellow solid	379.38
22	Ph	4-NO_2-Ph	53.4%	Yellow solid	379.38
23	4-t-Bu-Ph	2-OH-Ph	29.4%	Pale yellow solid	406.48
24	4-t-Bu-Ph	4-OH-Ph	24.1%	Pale brown solid	406.48
25	4-t-Bu-Ph	3-OH-2-Naphthyl	11.0%	Yellow solid	456.54
26	4-t-Bu-Ph	2,4-$(OH)_2$-Ph	27.5%	Pale yellow solid	422.48
27	4-t-Bu-Ph	3,4-$(OH)_2$-Ph	40.2%	Brown solid	422.48
28	4-t-Bu-Ph	2-NO_2-Ph	51.4%	Pale yellow solid	435.48

29	4-t-Bu-Ph	4-NO_2-Ph	49.9%	Yellow solid	435.48
30	4-CF_3-Ph	2-OH-Ph	48.5%	Yellow solid	418.37
31	4-CF_3-Ph	4-OH-Ph	60.0%	Pink solid	418.37
32	4-CF_3-Ph	3-OH-2-Naphthyl	8.2%	Pale yellow solid	468.43
33	4-CF_3-Ph	2,4-$(OH)_2$-Ph	3.1%	Brown solid	.434.37
34	4-CF_3-Ph	3,4-$(OH)_2$-Ph	73.2%	Pale pink solid	434.37
35	4-CF_3-Ph	2-NO_2-Ph	68.8%	Pale pink solid	447.37
36	4-CF_3-Ph	3-NO_2-Ph	64.2%	Pale yellow solid	447.37
37	4-CF_3-Ph	4-NO_2-Ph	60.1%	Pale yellow solid	447.37
38	4-I-Ph	2-OH-Ph	22.9%	Yellow solid	476.27
39	4-I-Ph	4-OH-Ph	36.6%	Pale brown solid	476.27
40	4-I-Ph	3-OH-2-Naphthyl	46.5%	Yellow solid	526.33
41	4-I-Ph	3,4-$(OH)_2$-Ph	52.5%	Pale pink solid	492.27
42	4-I-Ph	2-NO_2-Ph	43.3%	Pale pink solid	505.27
43	4-I-Ph	3-NO_2-Ph	51.4%	Yellow solid	505.27
44	4-I-Ph	4-NO_2-Ph	27.6%	Yellow solid	505.27
45	3-CF_3-Ph	2-OH-Ph	69.4%	Pale yellow solid	418.37
46	3-CF_3-Ph	4-OH-Ph	25.7%	Pale brown solid	418.37
47	3-CF_3-Ph	3-OH-2-Naphthyl	54.3%	Pale yellow solid	468.43

48	3-CF_3-Ph	2,4-$(OH)_2$-Ph	13.2%	Pale brown solid	434.37
49	3-CF_3-Ph	3,4-$(OH)_2$-Ph	57.3%	Pale pink solid	434.37
50	3-CF_3-Ph	2-NO_2-Ph	53.9%	Pink solid	447.37
51	3-CF_3-Ph	3-NO_2-Ph	57.4%	Pale yellow solid	447.37
52	3-CF_3-Ph	4-NO_2-Ph	32.2%	Pale yellow solid	447.37
53	3,4-Me_2-Ph	2-OH-Ph	52.2%	Pale yellow solid	378.43
54	3,4-Me_2-Ph	4-OH-Ph	66.2%	Pale pink solid	378.43
55	3,4-Me_2-Ph	3-OH-2-Naphthyl	65.9%	Pale yellow solid	428.49
56	3,4-Me_2-Ph	2,4-$(OH)_2$-Ph	43.0%	Pale yellow solid	394.43
57	3,4-Me_2-Ph	3,4-$(OH)_2$-Ph	40.4%	Pale yellow solid	394.43
58	3,4-Me_2-Ph	2-NO_2-Ph	67.9%	Pale yellow solid	407.43
59	3,4-Me_2-Ph	3-NO_2-Ph	50.8%	Pale yellow solid	407.43
60	3,4-Me_2-Ph	4-NO_2-Ph	67.1%	Pale brown solid	407.43
61	3,4-Cl_2-Ph	2-OH-Ph	45.6%	Pale yellow solid	419.27
62	3,4-Cl_2-Ph	4-OH-Ph	63.7%	Pale yellow solid	419.27
63	3,4-Cl_2-Ph	3-OH-2-Naphthyl	51.1%	Pale brown solid	469.33

64	3,4-Cl_2-Ph	2,4-$(OH)_2$-Ph	17.0%	Pale yellow solid	435.27
65	3,4-Cl_2-Ph	3,4-$(OH)_2$-Ph	66.1%	Pale pink solid	435.27
66	3,4-Cl_2-Ph	2-NO_2-Ph	67.4%	Pale yellow solid	448.27
67	3,4-Cl_2-Ph	3-NO_2-Ph	64.5%	Pale yellow solid	448.27
68	3,4-Cl_2-Ph	4-NO_2-Ph	51.1%	Brown solid	448.27
69	4-t-Bu-Ph	4-NH_2-Ph	74.8%	Pale brown solid	405.53
70	4-t-Bu-Ph	3-NH_2-Ph	48.7%	Pale brown solid	405.53
71	4-t-Bu-Ph	4-CF_3-Ph	69.1%	Pale yellow solid	458.49
72	4-t-Bu-Ph	4-t-Bu-Ph	77.9%	Pink solid	446.63
73	3,4-Me_2-Ph	4-NH_2-Ph	92.7%	Red solid	377.48
74	3,4-Me_2-Ph	3-NH_2-Ph	61.1%	Pale orange solid	377.48
75	3,4-Me_2-Ph	4-CF_3-Ph	67.7%	Pale orange solid	430.44
76	3,4-Me_2-Ph	4-t-Bu-Ph	66.8%	Pale pink solid	418.58
77	3,4-Cl_2-Ph	4-NH_2-Ph	51.2%	Orange solid	418.32
78	3,4-Cl_2-Ph	3-NH_2-Ph	69.7%	Pink solid	418.32
79	3,4-Cl_2-Ph	4-CF_3-Ph	69.6%	Pale orange solid	471.28
80	3,4-Cl_2-Ph	4-t-Bu-Ph	79.8%	Pale pink solid	459.42
81	4-t-Bu-Ph	3-OH-Ph	72.3%	Pale yellow solid	406.53

82	3,4-Me_2-Ph	3-OH-Ph	42.0%	Pale pink solid	378.48
83	3,4-Cl_2-Ph	3-OH-Ph	89.0%	Pink solid	419.32
84	3-NO_2-Ph	3-NO_2-Ph	58%	Brown solid	424.57
85	2-Py	3-NO_2-Ph	63%	Pale orange solid	380.36
86	3-NO_2-Ph	2,4-$(OH)_2$-Ph	43%	Brown solid	411.37
87	2-Py	2,4-$(OH)_2$-Ph	66%	Pale yellow solid	367.36
88	3-NO_2-Ph	4-t-Bu-Ph	25%	Brown solid	435.48
89	3-CF_3-Ph	3-NH_2-Ph	74%	Pale brown solid	417.38
90	3-CF_3-Ph	4-NH_2-Ph	82%	Pale orange solid	417.38
91	4-CF_3-Ph	3-NH_2-Ph	69%	Brown solid	417.38
92	4-CF_3-Ph	4-NH_2-Ph	72%	Pale pink solid	417.38

SYNTHETIC EXAMPLE 93

Synthesis of 2,4-dihydroxybenzoic N'-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide

1) Synthesis of 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde

1.86 g (9.16 mmol) of 1-(3,4-dimethylphenyl)-3-methyl-3-pyrazolin-5-one was dissolved in 3.6 ml of dry dimethylformamide, and 1.02 ml (11.0 mmol) of phosphorus oxychloride was added gradually under cooling with ice at

20°C or below. After the addition, the mixture was heated at 100°C for 2 hours, cooled to room temperature and poured into 30 ml of ice-cold water. Then, the mixture was washed with 10 ml of water and 10 ml of dimethylformamide. The mixed solution was stirred for 18 hours, and the precipitated solid was collected by filtration, washed with 20 ml of water and dried to obtain 1.03 g of the desired product as a pale brown solid (yield 49%).

^{1}H-NMR (ppm in $CDCl_3$)

δ = 2.29 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H, J = 8 Hz), 7.48 (dd, 1H, J = 8 Hz, 2 Hz), 7.54 (d, 1H, J = 2 Hz), 9.60 (s, 1H)

2) Synthesis of 2,4-dihydroxybenzoic N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl]-hydrazide

46 mg (0.2 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) and 34 mg (0.20 mmol) of 2,4-dihydroxybenzoic hydrazide were stirred in 1 ml of ethanol at room temperature for 96 hours. The precipitated solid was collected by filtration and washed with 1 ml of ethanol, 1 ml of ether and 1 ml of methanol successively to obtain 53 mg of the desired product (yield 70%).

LC/MS

M^+ = 380.40 (2.77 min)

SYNTHETIC EXAMPLE 94

Synthesis of 2,4-dihydroxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1-(5-Hydroxy-3-methyl-1-(3-trifluoromethylphenyl-1H-pyrazol-4-yl)-ethanone (0.173 mmol, 51.5 mg) and 2,4-dihydroxybenzoic hydrazide (0.173 mmol, 30.6 mg) were stirred in ethanol (5 ml) at 80°C for 19 hours. After the solvent was removed by evaporation, the residue was dried with a vacuum pump and filtered with chloroform, and the filtrate was concentrated and resolved by silica gel thin layer chromatography ($CHCl_3$/MeOH = 10/1) to obtain 2,4-dihydroxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide as a pale yellow solid (67 mg, yield 87%, purity 80.7%).

LC-MS 448.40 (M^+)

SYNTHETIC EXAMPLE 95

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1-(5-Hydroxy-3-methyl-1-(3-trifluoromethylphenyl)-1H-pyrazol-4-yl)-ethanone (0.189 mmol, 56.5 mg) and 4-methoxycarbonylbenzhydrazide (0.189 mmol, 36.8 mg) were stirred in DMF at 100°C for 2.2 hours and at 120°C for 17 hours. After the solvent was removed by evaporation, the residue was resolved by silica gel thin layer

chromatography ($CHCl_3$/MeOH = 10/1) to obtain 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide as a yellow solid (55.6 mg, 62%)

LC-MS 474.43 (M^+)

SYNTHETIC EXAMPLE 96

Synthesis of 4-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

4-Methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (0.107 mmol, 50.7 mg) was dissolved in methanol (2 ml) and stirred with 1M aqueous sodium hydroxide (0.534 mmol, 0.534 ml) at room temperature for 2 hours and at 60°C for 1.5 hours. Then, the reaction vessel was cooled to 0°C, and 1M hydrochloric acid (0.534 mmol, 0.534 ml) and water were added. The precipitated solid was collected by filtration with water and dried to obtain 4-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-trifluoromethyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide as a yellow solid (43.8 mg, 89%).

LC-MS 460.41 (M^+)

SYNTHETIC EXAMPLE 97

Synthesis of 4-carboxy-benzoic N'-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide

1) Synthesis of 1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde

1.89 g (9.33 mmol) of 1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazole was dissolved in 3.6 ml of dry dimethylformamide, and 1.05 ml (11.26 mmol) phosphorus oxychloride was added gradually at 20°C or below under cooling with ice. After the addition, the mixture was heated at 100°C for 3 hours, then cooled to room temperature and poured into 30 ml of ice-cold water. The mixed solution was stirred at room temperature for 18 hours, and the precipitated solid was collected by filtration, washed with 20 ml of water and dried to obtain 1.61 g of the above-identified desired product as a yellow solid (yield 70%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.30-1.33 (m, 9H), 2.34-2.44 (m, 3H), 7.48-7.62 (m, 4H), 9.62-9.90 (m, 1H).

2) Synthesis of 4-methoxycarbonyl-benzoic N'-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide

1.0712 g (4.21 mmol) of the 1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) and 819.6 mg (4.22 mmol) of 4-methoxycarbonylbenzhydrazide were stirred in 10 ml of dimethylformamide at room temperature for 3 hours. After the solvent was removed by evaporation, the precipitated solid was washed with a small amount of methanol and

dried to obtain 765.9 mg of the above-identified desired product as a yellow solid (yield 42%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.30 (s, 9H), 2.19-2.21 (m, 3H), 3.90 (s, 3H), 7.33 (s, 1H), 7.40-7.46(m, 2H), 7.81-7.89(m, 2H), 8.01-8.17(m, 4H).

3) Synthesis of 4-carboxy-benzoic N'-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide

59.4 mg (0.14 mmol) of the 4-methoxycarbonyl-benzoic N'-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide synthesized in 2) was dissolved in 5.0 ml of methanol and stirred with 0.68 ml (0.68 mmol) of 1M aqueous sodium hydroxide at room temperature for 6 hours and then at 60°C for 3 hours. After the stirring, 0.68 ml (0.68 mmol) of hydrochloric acid was added, and the precipitated solid was collected by filtration and dried to obtain 33.3 mg of the above-identified desired product as a yellow solid (yield 58%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.30 (s, 9H), 2.19-2.21 (m, 3H), 7.33 (s, 1H), 7.40-7.46 (m, 2H), 7.80-7.89 (m, 2H), 7.99-8.14 (m, 4H).

LC/MS

M^+ = 420.46 (2.39 min)

SYNTHETIC EXAMPLE 98

Synthesis of 5-methoxycarbonyl-2-thiophenecarboxylic acid N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-

dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1) Synthesis of 5-methoxycarbonyl-2-thiophenecarboxylic acid

1.72 g (10 mmol) of thiophene-2,5-dicarboxylic acid and 3.18 g (30 mmol) of sodium carbonate suspended in 25 mL of DMF were stirred with 623 μL of methyl iodide at room temperature overnight. The sodium salt of the desired product was extracted with water, and 12M of hydrochloric acid was added to the combined aqueous layer. The desired product was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous ammonium chloride and dried over anhydrous magnesium sulfate. The desired product was purified by silica gel column chromatography to give 0.49 g of a colorless solid (yield 28%).

^{1}H-NMR (ppm in $CDCl_3$)

δ = 3.93 (s, 3H), 7.77 (d, 1H, J = 4.2 Hz), 7.83 (d, 1H, J = 4.2 Hz).

LC/MS

M^+ = 186 (0.92 min)

2) Synthesis of 5-methoxycarbonyl-2-thiophenecarboxylic acid hydrazide

The known procedure disclosed in the literature (J. Heterocyclic Chem., 28, 17, (1991).) was followed using 5-methoxycarbonyl-2-thiophenecarboxylic acid, thionyl chloride and hydrazine monohydrate to give 144 mg of a white solid (yield 72%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 3.84 (s, 3H), 4.57 (brs, 2H), 7.72 (d, 1H, J = 4.2 Hz), 7.79 (d, 1H, J = 4.2 Hz), 10.06 (brs, 1H).

LC/MS

M^+ = 200 (3.09 min)

3) Synthesis of 5-methoxycarbonyl-2-thiophenecarboxylic acid N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

54.5 mg (0.20 mmol) of 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 40.0 mg (0.20 mmol) of 5-methoxycarbonyl-2-thiophenecarboxylic acid hydrazide were dissolved in 2.0 mL of DMF and stirred at 110°C for 12 hours. After cooling, the solvent was removed by evaporation, and the crude product was washed with ethyl acetate and collected by filtration to obtain 32.0 mg of the desired product as a yellow solid (yield 35%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.29 (s, 9H), 2.36 (s, 3H), 2.43 (s, 3H), 3.87 (s, 3H), 7.41 (d, 2H, J = 9.0 Hz), 7.87-7.90 (m, 4H).

LC/MS

M^+ = 454.54 (4.46 min)

SYNTHETIC EXAMPLE 99

Synthesis of 5-carboxy-2-thiophenecarboxylic acid N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

14.9 mg (0.033 mmol) of 5-methoxycarbonyl-2-

thiophenecarboxylic acid N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide in 1.5 mL of methanol was stirred with 164 μL (0.164 mmol) of 1M aqueous sodium hydroxide at room temperature for 17 hours. After the stirring, 164 μL (0.164 mmol) of 1M hydrochloric acid was added, and the precipitated solid was collected by filtration to obtain 6.8 mg of the desired product as a pale yellow solid (yield 47%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.29 (s, 9H), 2.36 (s, 3H), 2.43 (s, 3H), 7.41 (d, 2H, J = 9.0 Hz), 7.80 (d, 1H, J = 3.9 Hz), 7.87-7.90 (m, 3H).

LC/MS

M^+ = 440.52 (4.23 min)

SYNTHETIC EXAMPLE 100

Synthesis of 4-carboxy-benzoic N'-(1-(1-(quinolin-2-yl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

1) Synthesis of 4-methoxycarbonyl-benzoic N'-(1-(1-(quinolin-2-yl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (compound)

2.0 mL of an isopropyl alcohol solution of 28.7 mg (0.11 mmol) of 1-(1-(quinolin-2-yl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone, 20.8 mg (0.11 mmol) of 4-methoxycarbonylbenzhydrazide and 6.1 mg (0.03 mmol) of p-toluenesulfonic acid monohydrate was refluxed with heating for 48 hours. After cooling, the precipitate was

collected by filtration and washed with methanol and acetonitrile to obtain 14.9 mg of the desired product as a purple solid (yield 31%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 2.54 (s, 3H), 3.91 (s, 3H), 7.58-7.63 (m, 1H), 7.80-7.85 (m, 1H), 8.01-8.15 (m, 6H), 8.46 (d, 1H, J = 6.3 Hz), 8.58 (d, 1H, J = 6.3 Hz).

LC/MS

M^+ = 443.45 (3.21 min)

2) Synthesis of 4-carboxy-benzoic N'-(1-(1-quinolin-2-yl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (compound)

1.5 mL of a methanol solution of 14.9 mg (0.034 mmol) of the 4-methoxycarbonyl-benzoic N'-(1-(1-(quinolin-2-yl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in 1) was stirred with 168 μL (0.168 mmol) of 1M aqueous sodium hydroxide at 50°C for 12 hours. After the stirring, 168 μL (0.168 mmol) of 1M hydrochloric acid was added, and the precipitated solid was collected by filtration to obtain 4.9 mg of the desired product as a dark yellow solid (yield 34%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 2.44 (s, 3H), 7.52-7.56 (m, 1H), 7.75 (t, 1H, J = 7.5 Hz), 7.94 (d, 1H, J = 4.5 Hz), 7.96 (d, 1H, J = 4.2 Hz), 8.05 (d, 2H, J = 8.7 Hz), 8.10 (d, 2H, J = 8.4 Hz), 8.33 (d, 1H, J = 9.6 Hz), 8.42 (d, 1H, J = 9.0 Hz).

LC/MS

M^+ = 429.43 (3.21 min)

SYNTHETIC EXAMPLE 101

Synthesis of methyl 4-[(2-{1-[1-(6-chloro-3-pyridazinyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl]ethylidene}hydrazino)carbonyl]benzoate

0.2 mmol of 1-[1-(6-chloro-3-pyridazinyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl]ethanone and 0.2 mmol of 4-methoxycarbonylbenzhydrazide were dissolved in 2 ml of DMSO and heated at 100°C for 8 hours with stirring. After the solvent was removed by evaporation, the crude product was dissolved in chloroform and recrystallized from ether to obtain 55 mg of the desired product, methyl 4-[(2-{1-[1-(6-chloro-3-pyridazinyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl]ethylidene}hydrazino)carbonyl]benzoate (yield 64%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.42 (s, 3H), 2.54 (s, 3H), 3.91 (s, 3H), 7.96 (d, 1H, J = 9.3 Hz), 8.06 (d, 2H, J = 8.4 Hz), 8.13 (d, 2H, J = 8.4 Hz), 8.44 (d, 1H, J = 9.3 Hz).

LC/MS

M^+ = 428.83 (2.88 min).

SYNTHETIC EXAMPLE 102

Synthesis of 4-{[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethylidene)hydrazino]carbonyl]benzoic acid

1) Synthesis of methyl 4-{[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-

yl}ethylidene)hydrazino]carbonyl}benzoate

0.2 mmol of 1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethanone and 0.2 mmol of 4-methoxycarbonylbenzhydrazide were heated in 2 ml of DMF at 100°C for 9 hours with stirring. After the solvent was removed by evaporation, the resulting crude product was dissolved in chloroform and recrystallized from hexane to obtain 66 mg of the desired product, methyl 4-{[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethylidene)hydrazino]carbonyl}benzoate (yield 72%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.41 (s, 3H), 2.50 (s, 3H), 3.88 (s, 3H), 7.9-8.4 (m, 6H), 8.80 (s, 1H).

LC/MS

M^+ = 461.39 (3.00 min).

2) Synthesis of {4-[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethylidene)hydrazino]carbonyl}benzoic acid

50 mg of the methyl 4-{[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}ethylidene)hydrazino]carbonyl}benzoate synthesized in 1) was heated in 3 ml of methanol and 0.3 ml of 1M aqueous sodium hydroxide at 60°C for 8 hours with stirring. After it was cooled to room temperature, 0.3 ml of 1M hydrochloric acid was added to precipitate crystals, and crystals were collected by filtration and

dried to obtain 30 mg of the desired product, 4-{[2-(1-{5-hydroxy-3-methyl-1-[5-(trifluoromethyl)-2-pyridinyl]-1H-pyrazol-4-yl}-ethylidene)hydrazino]carbonyl}benzoic acid as a pale brown solid (yield 62%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.41 (3H, s), 2.50 (3H, s), 8.04 (d, 2H, J = 8.4 Hz), 8.10(d, 2H, J = 8.4 Hz), 8.26 (dd, 1H, J = 9 Hz, J = 2.4 Hz), 8.35 (d, 1H, J = 9 Hz), 8.81 (brs, 1H), 11.6 (brs, 1H), 12.4 (brs, 1H)

LC/MS

M^+ = 447.37 (2.65 min).

SYNTHETIC EXAMPLE 103

Synthesis of 4-(1H-tetrazol-5-yl)-benzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

A DMF solution (1 ml) of 27.2 mg (0.10 mmol) of 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 20.4 mg (0.10 mmol) of 4-(1H-tetrazol-5-yl)-benzoic hydrazide synthesized by the method disclosed in WO03/037328 was heated at 60°C for 6 hours with one drop of concentrated hydrochloric acid, and the precipitated solid was washed with water and collected by filtration. The solid was mixed with 1M aqueous sodium hydroxide and filtered. 1M Hydrochloric acid was added to the filtrate, and the precipitated solid was collected by filtration to obtain 5.9 mg of the desired product as a brown solid (yield 12%).

^{1}H-NMR (ppm in DMSO- d_6)

δ = 1.30 (s, 9H), 2.38 (s, 3H), 2.47 (s, 3H), 7.42 (d, 2H, J = 8.6 Hz), 7.90 (d, 2H, J = 8.6 Hz), 8.14 (d, 2H, J = 8.4 Hz), 8.23 (d, 2H, J = 8.4 Hz).

LC/MS

M^+ = 458.52 (2.62 min)

REFERENCE SYNTHETIC EXAMPLE 1 (EXAMPLE 4 OF WO01/34585)

Synthesis of 5-(4-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

1) Synthesis of 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde

1.86 g (9.16 mmol) of 1-(3,4-dimethylphenyl)-3-methyl-3-pyrazolin-5-one was dissolved in 3.6 ml of dry dimethylformamide, and 1.02 ml (11.0 mmol) of phosphorus oxychloride was added gradually under cooling with ice at 20°C or below. After the addition, the mixture was heated at 100°C for 2 hours, then cooled to room temperature and poured into 30 ml of ice-cold water. Then, it was washed with 10 ml of water and 10 ml of dimethylformamide. The mixed solution was stirred for 18 hours, and the precipitated solid was collected by filtration, washed with 20 ml of water and dried to obtain 1.03 g of the above-identified desired product as a pale brown solid (yield 49%).

^{1}H-NMR (ppm in $CDCl_3$)

δ = 2.29 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H,

J = 8 Hz), 7.48 (dd, 1H, J = 8 Hz, 2Hz), 7.54 (d, 1H, J = 2 Hz), 9.60 (s, 1H)

2) Synthesis of 5-(4-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

230 mg (1 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) and 148 mg (1 mmol) of 3-aminorhodanine were stirred in 10 ml of ethanol at room temperature for 96 hours. The resulting solid was collected by filtration, washed with ethanol and ether and dried to obtain 332 mg of a crude imine.

A liquid mixture of 160 mg (0.444 mmol) of the imine, 4 mg of piperidine, 66 mg of 4-formylbenzoic acid, 6 mg of benzoic acid and 20 ml of toluene was refluxed in a reactor equipped with a Dean-Stark tube packed with molecular sieve for 7 hours with heating. After cooling, the precipitated solid was collected by filtration and washed with 3 ml of toluene and 3 ml of ether to obtain 23.3 mg of a yellow solid. It was washed with a liquid mixture of methanol and chloroform to obtain 16.5 mg of the desired product (yield 7.5%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.10-2.40 (s×3, 9H), 7.18(d, 1H, J = 8 Hz), 7.63 (d, 1H, J = 8 Hz), 7.67 (s, 1H), 7.84 (d, 2H, J = 8 Hz), 8.03 (d, 2H, J = 8 Hz), 8.10 (d, 2H, J = 8 Hz), 8.20 (s, 1H)

LC/MS

M^+ = 493.0 (3.33 min)

REFERENCE SYNTHETIC EXAMPLE 2 (EXAMPLE 5 OF WO01/34585)

Synthesis of 5-(3-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

A liquid mixture of 160 mg (0.444 mmol) of the imine synthesized in 2) of Reference Synthetic Example 1, 4 mg of piperidine, 66 mg of 3-formylbenzoic acid, 6 mg of benzoic acid and 20 ml of toluene was refluxed in a reactor equipped with a Dean-Stark tube packed with molecular sieve for 7 hours with heating. After cooling, the precipitated solid was collected by filtration and washed with 3 ml of toluene and 3 ml of ether to obtain 38.5 mg of a yellow solid (yield 18%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.00-2.30 (s×3, 9H), 7.18 (d, 1H, J = 8 Hz), 7.64 (d, 1H, J = 8 Hz), 7.68 (s, 1H), 7.73 (t, 1H, J = 8 Hz), 7.97 (d, 2H, J = 8 Hz), 8.06 (s, 1H), 8.08 (d, 1H, J = 8 Hz), 8.23 (d, 2H, J = 8 Hz)

LC/MS

M^+ = 493.0 (3.32 min)

REFERENCE SYNTHETIC EXAMPLE 3 (EXAMPLE 2 OF WO01/34585)

Synthesis of 3-(3-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

1) Synthesis of 1-amino-3-(3-carboxyphenyl)-2-thioxoimidazolidin-4-one

179 mg (1 mmol) of 3-isothiocyanatobenzoic acid and 523 µl (3 mmol) of diisopropylethylamine were stirred in 8 ml of dichloromethane and then with 155 mg (1 mmol) of ethyl hydrazinoacetate hydrochloride at room temperature for 96 hours. After the solvent was concentrated, the mixture was partitioned between ethyl acetate and 30% acetic acid. The aqueous layer was extracted with ethyl acetate again, and the organic layers were combined, washed with water and then with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated. The resulting solid was mixed with a 190:10:0.8 liquid mixture of ethyl acetate, methanol and acetic acid, and the insoluble was dried to obtain 55.7 mg of the desired product (yield 22%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 4.44 (s, 2H), 5.46 (s, 2H), 7.57 (dd, 1H, J = 8 Hz, J = 1.5 Hz), 7.63 (t, 1H, J = 8 Hz), 7.90 (s, 1H), 7.99(d, 1H, J = 8 Hz)

LC/MS

M^+ = 251.30 (0.59 min).

2) Synthesis of 3-(3-caboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

50 mg (0.2 mmol) of the 1-amino-3-(3-carboxyphenyl)-2-thioxoimidazolidin-4-one synthesized above in 1) and 55 mg (0.22 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) of

Reference Synthetic Example 1 were stirred in a liquid mixture of 10 ml of ethanol and 5 ml of methanol at room temperature for 96 hours. The resulting insoluble was collected by filtration to obtain 73 mg of the desired product as a yellow solid (yield 72%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.24 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 4.74 (s, 2H), 7.21 (d, 1H, J = 8 Hz), 7.40-7.80 (m, 4H), 7.95 (s, 1H), 8.02 (d, 1H, J = 8 Hz), 8.14 (s, 1H)

LC/MS

M^+ = 463.51 (2.77 min).

REFERENCE SYNTHETIC EXAMPLE 4 (EXAMPLE 3 OF WO01/34585)

Synthesis of 3-(4-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

1) Synthesis of 1-amino-3-(4-carboxyphenyl)-2-thioxoimidazolidin-4-one

179 mg (1 mmol) of 4-isothiocyanatobenzoic acid and 523 µl (3 mmol) of diisopropylethylamine were stirred in 8 ml of dichloromethane and then with 155 mg (1 mmol) of ethyl hydrazinoacetate hydrochloride at room temperature for 96 hours. After the solvent was concentrated, the mixture was partitioned between ethyl acetate and 30% acetic acid. The aqueous layer was extracted with ethyl acetate again, and the organic layers were combined, washed with water and then with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated.

The resulting solid was mixed with a 190:10:0.8 liquid mixture of ethyl acetate, methanol and acetic acid, and the insoluble was dried to obtain 132 mg of the desired product (yield 53%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 4.46(s, 2H), 5.47 (s, 2H), 7.46 (d, 2H, J = 8 Hz), 8.04 (d, 2H, J = 8 Hz)

LC/MS

M^+ = 251.26 (0.95 min).

2) Synthesis of 3-(4-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

50 mg (0.2 mmol) of the 1-amino-3-(4-carboxyphenyl)-2-thioxoimidazolidin-4-one synthesized above in 1) and 55 mg (0.22 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) of Reference Synthetic Example 1 were stirred in a liquid mixture of 10 ml of ethanol and 5 ml of methanol at room temperature for 96 hours. The resulting insoluble was collected by filtration to obtain 87 mg of the desired product as a yellow solid (yield 85%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.24 (s, 3H), 2.27 (s, 3H), 2.50 (s, 3), 4.75 (s, 2H), 7.21 (d, 1H, J = 8 Hz), 7.40-7.70 (m, 4H), 8.08 (d, 2H, J = 8.8 Hz), 8.14 (brs, 1H)

LC/MS

M^+ = 463.51 (2.76 min).

The structural formulae of the compounds obtained in the Synthetic Examples are as follows.

【Ka 18】

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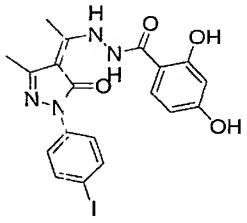

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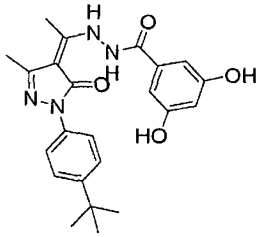

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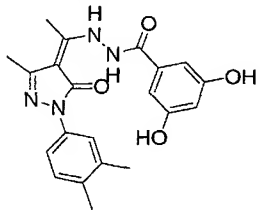

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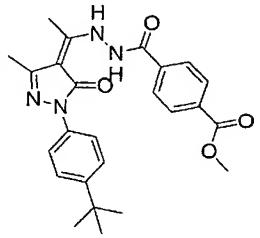

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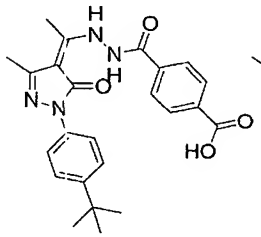

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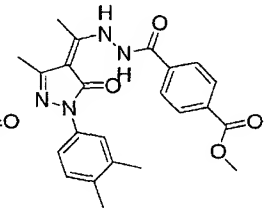

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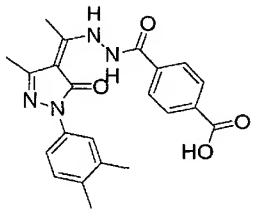

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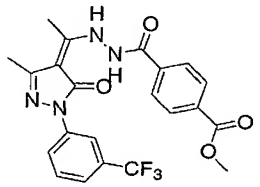

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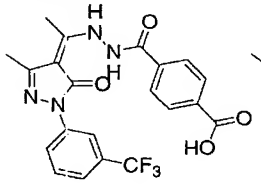

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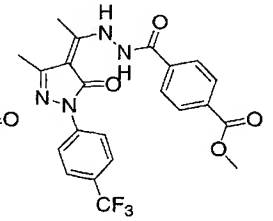

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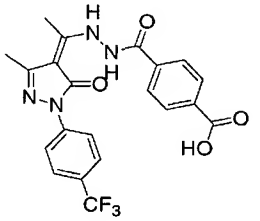

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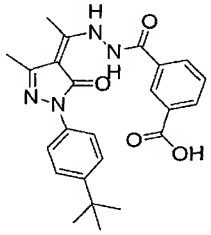

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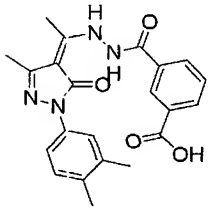

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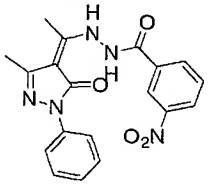

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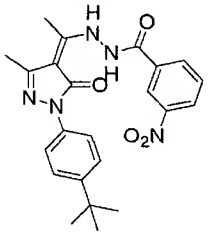

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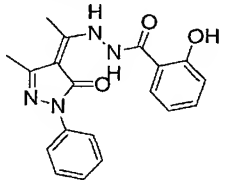

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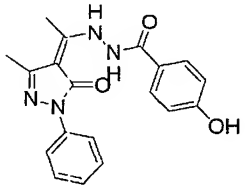

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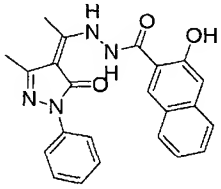

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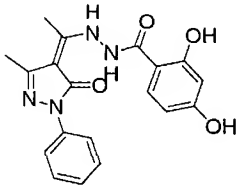

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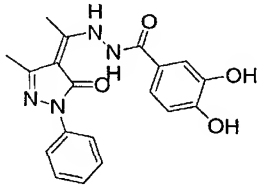

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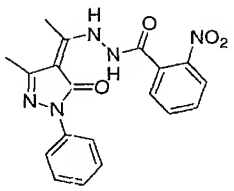

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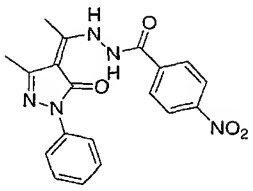

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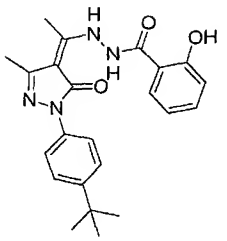

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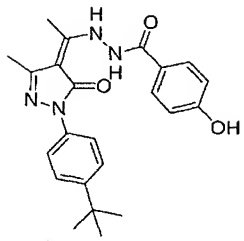

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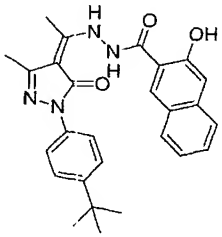

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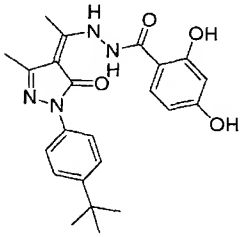

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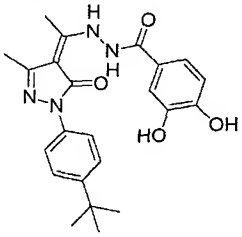

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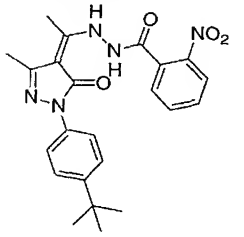

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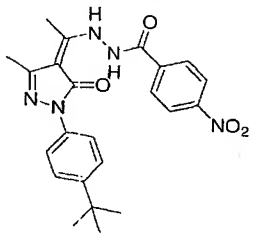

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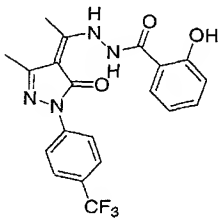

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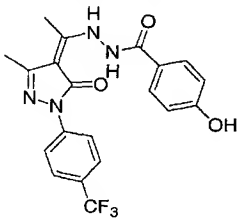

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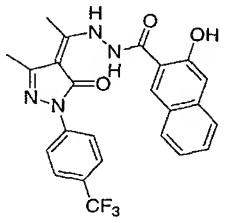

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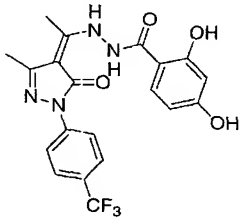

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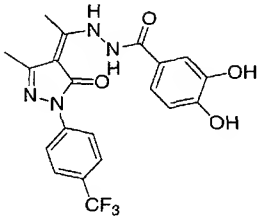

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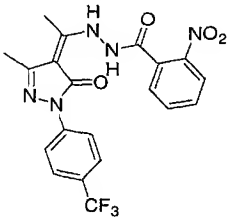

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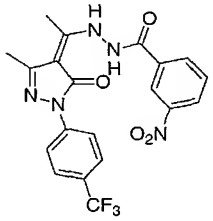

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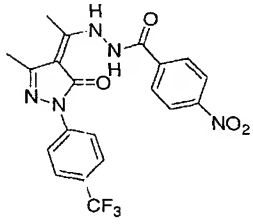

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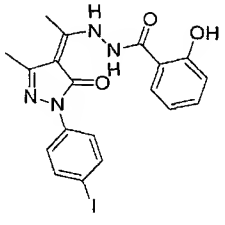

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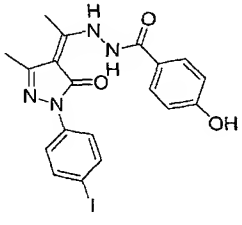

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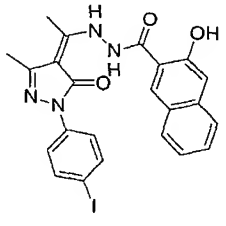

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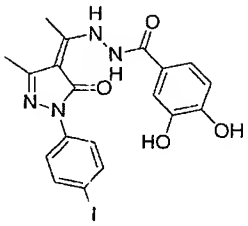

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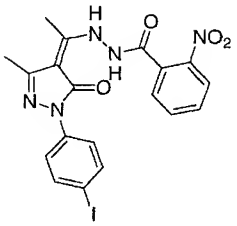

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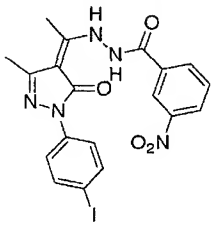

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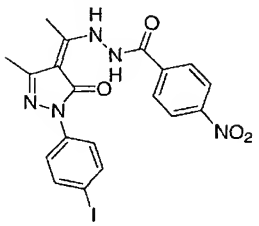

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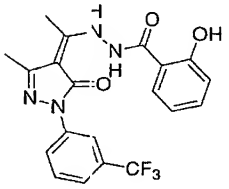

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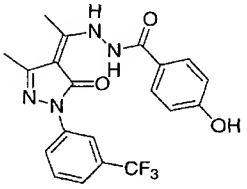

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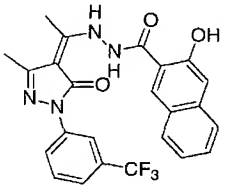

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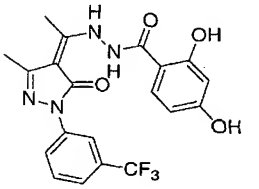

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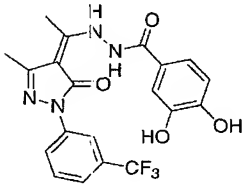

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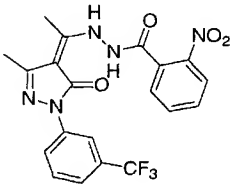

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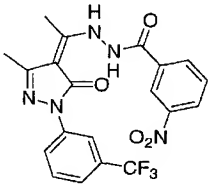

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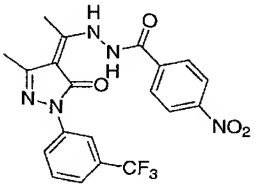

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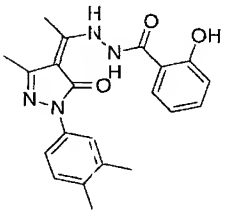

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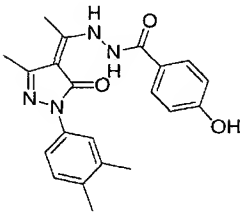

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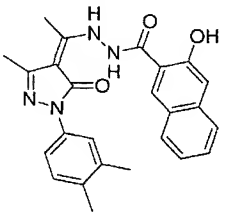

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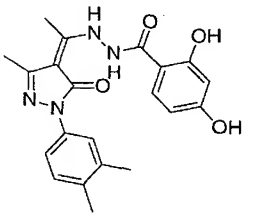

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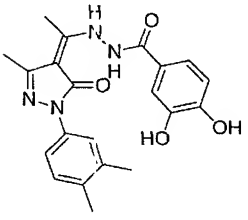

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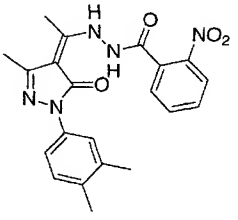

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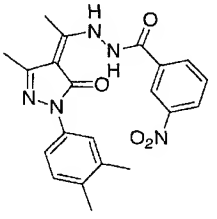

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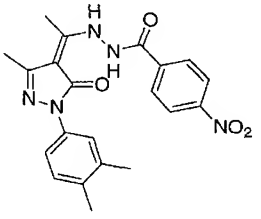

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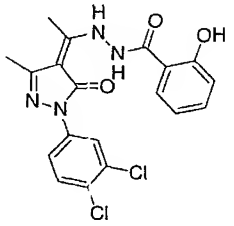

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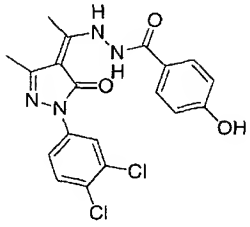

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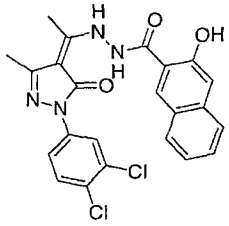

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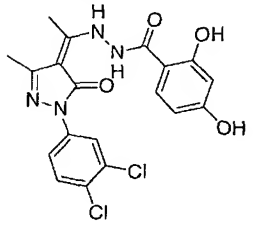

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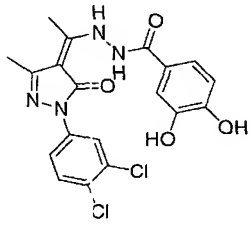

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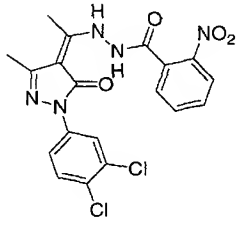

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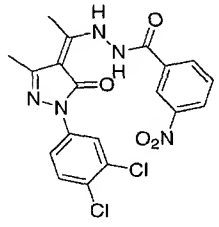

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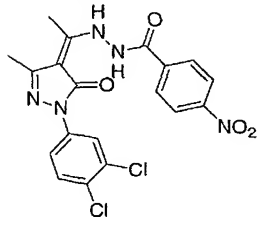

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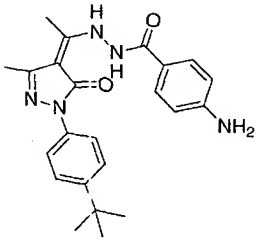

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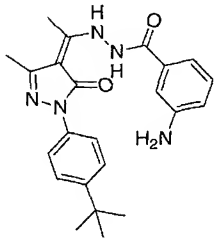

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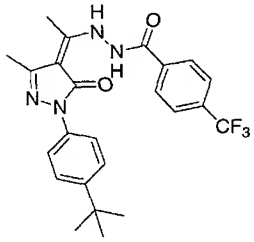

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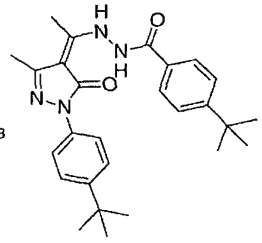

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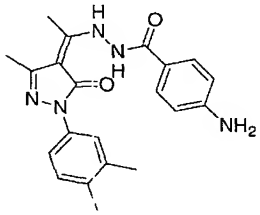

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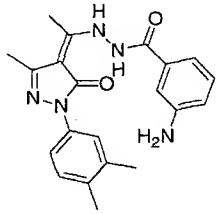

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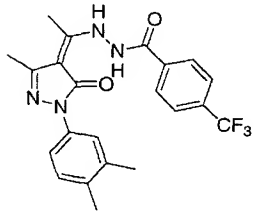

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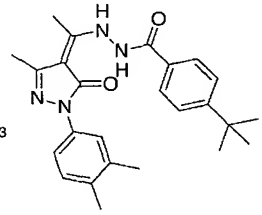

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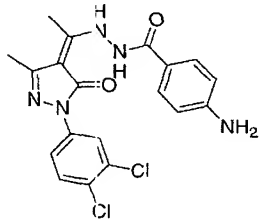

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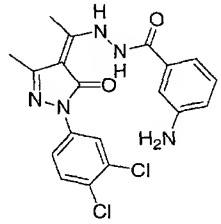

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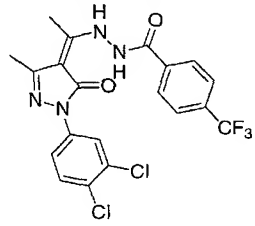

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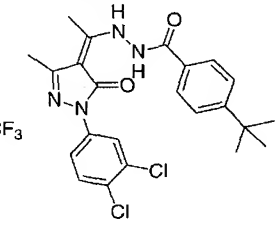

【Ka 22】

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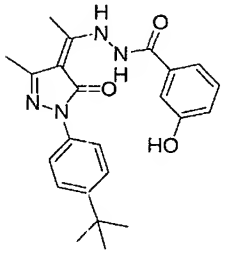

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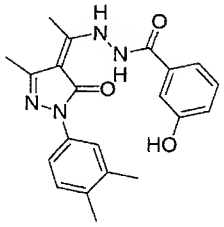

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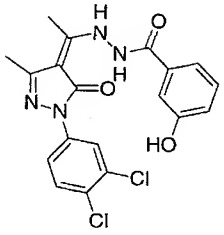

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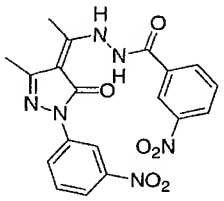

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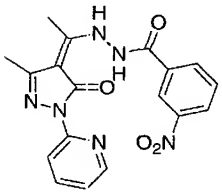

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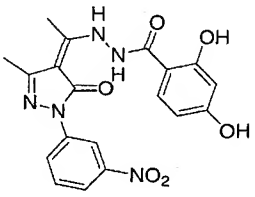

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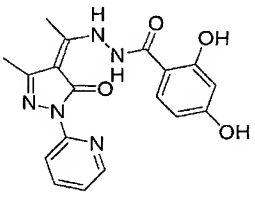

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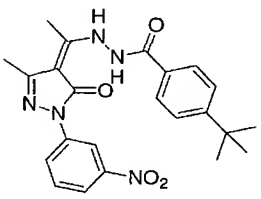

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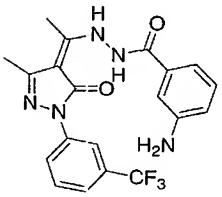

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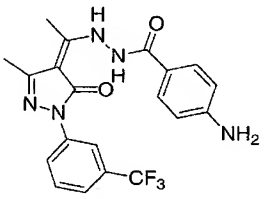

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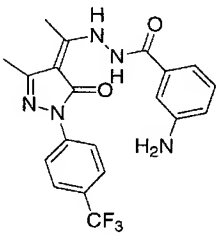

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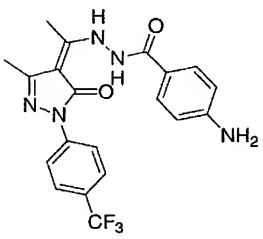

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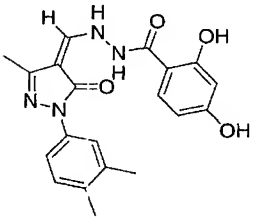

【Ka 23】

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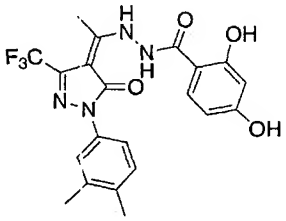

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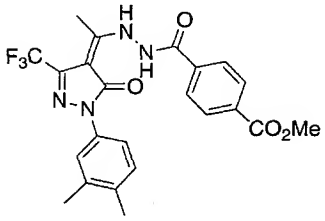

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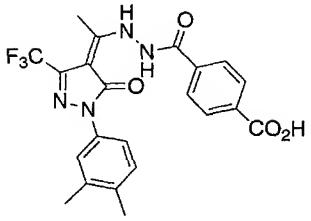

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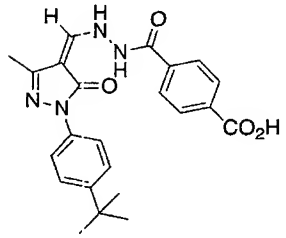

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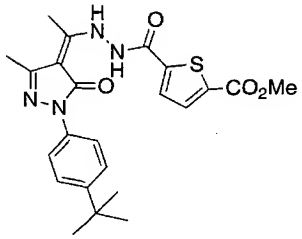

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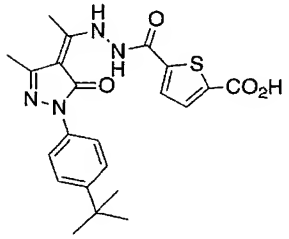

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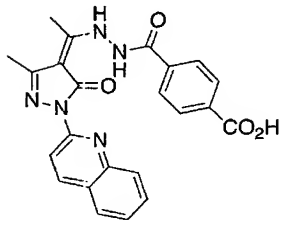

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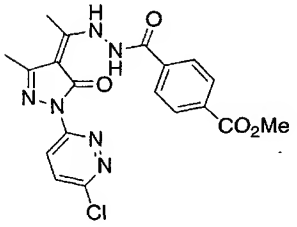

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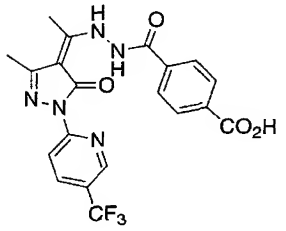

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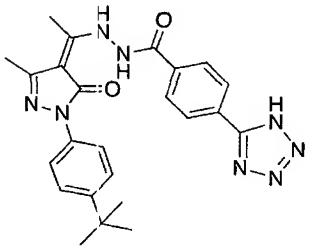


ASSAY EXAMPLE 1

Stimulation of Proliferation of a Thrombopoietin (TPO)-dependent Cell Line (1)

The reactivity of Synthetic Example 56, the compound of the present invention, with thrombopoietin (TPO) receptor was assayed using a human leukemic cell line, UT7/EPO-mpl.

(1) Cells and cell culture

UT7/EPO-mpl is a stable transformed cell line obtained by introducing into human leukemic cell line UT7/EPO a vector that induces expression of human thrombopoietin receptor (*c-mpl*) under control of a cytomegaloviral promoter by the method of Takatoku et al. (J. Biol. Chem., 272:7259-7263 (1997)). Proliferation of this cell line is stimulated by thrombopoietin, while its mother cell line UT7/EPO exhibits no response to thrombopoietin. These two cell lines were subcultured in IMDM (GIBCO) containing 10% fetal bovine serum (TRACE SCIENTIFIC) using a CO_2 incubator (5% CO_2, 37°C).

(2) Cell proliferation assay by the MTT method

The subcultured cells described above were washed twice with PBS and suspended in IMDM containing 10% fetal bovine serum at a cell density of 6×10^4 cells/ml. The cell suspension was transferred to a 96-well tissue culture plate (CORNING) in 100-µl aliquots. Then Synthetic Example 56 dissolved in DMSO was diluted 83-fold with IMDM containing 10% fetal bovine serum and added to the aforementioned cell suspension in 20-µl aliquots. The suspension was incubated in a CO_2 incubator (5% CO_2, 37°C) for 4 days. Cell proliferation

was assayed according to the method of Mosmann et al. (J. Immunological Methods, 65:55-63 (1983)). A 10-µl aliquot of 5 mg/ml MTT reagent (SIGMA) was added to each well of the tissue culture plate, and the plate was incubated at 37°C for 4 h. The formazan pigment generated was dissolved by adding 150 µl per well of 0.1 M HCl/isopropanol solution and the absorbance of the resulting pigment solution was measured at 550 nm with a 96-well microplate reader (BIO-RAD, M450). Figure 1 shows the results with UT7/EPO-mpl cells, while Figure 2 shows data obtained with UT7/EPO cells expressing no thrombopoietin receptor.

Figure 1 demonstrated that proliferation of UT7/EPO-mpl cells was stimulated by Synthetic Example 56 in a concentration-dependent manner, while no effect of this compound on proliferation was observed with UT7/EPO, the mother cell line, as shown in Figure 2.

ASSAY EXAMPLE 2

Activity of Signal Transduction Mediated by Thrombopoietin Receptor

The signal-transducing activity of Synthetic Example 56, the compound of the present invention, mediated by thrombopoietin receptor was assayed according to the method of Komatsu et al. (Blood, 87:4552-4560 (1996)). Human leukemic cell line UT7/EPO-mpl was washed three times with PBS and suspended in IMDM (GIBCO) containing 10% fetal bovine serum (TRACE SCIENTIFIC) at a cell

density of 9×10^5 cells/ml. The cell suspension was incubated in a CO_2 incubator (5% CO_2, 37°C) for 18 h. To 2 ml of this cell suspension (7×10^6 cells/ml), either thrombopoietin (final concentration, 30 ng/ml) or a DMSO solution of Synthetic Example 56 (final concentration, 1 µg/ml) was added. After incubating the mixture at 37°C for 1-15 min, the cells were lysed in 1.4 ml of TNE buffer [20 mM Tris-HCl buffer (pH 7.4) containing 150 mM NaCl, 1 mM EDTA, 1% Triton X-100, 1 mM PMSF, 1 mM Na_3VO_4, and 1/400-diluted Protease inhibitor cocktail (SIGMA)]. The cell lysate was centrifuged to collect the supernatant for immunoprecipitation with antibodies against proteins involved in signal transduction [anti-STAT3 (SANTACRUZ BIOTECHNOLOGY) and anti-STAT5A (UPSTATE BIOTECHNOLOGY)] and protein G Sepharose (PHARMACIA). The immunoprecipitated protein fraction was collected and denatured in a sample buffer for separation by SDS-polyacrylamide gel electrophoresis (7.5%). The separated proteins were transferred onto PVDF membrane (ATTO, 0.2 µm) at 100 V for 1 h for detection of tyrosine phosphorylation using an alkaline phosphatase-labelled antibody against phosphorylated tyrosine (RC20, TRANSDUCTION LABORATORIES). The antigen-antibody complex formed on the PVDF membrane was visualized with 150 µg/ml NBT (BIO-RAD) and 300 µg/ml BCIP (BIO-RAD). The results are summarized in Table 7.

Table 7

	DMSO	SYNTHETIC EXAMPLE No. 56	Thrombopoietin
STAT 3	-	+	+
STAT 5A	-	+	+

ASSAY EXAMPLE 3

The following Synthetic Examples were tested according to the method of Assay Example 1 to determine the maximal growth rate (Efficacy), expressed by taking the value with human leukemic cell line UT7/EPO-mpl observed in the presence of 10 ng/ml TPO as 100% standard, and the concentration of each compound that yields a growth rate corresponding to 50% of the maximum cell growth observed with the same compound (EC_{50}). The results are summarized in Table 8. (Here, "-" indicates that EC_{50} was not determined because the value of Efficacy was below the detection limit.

Table 8

Synthetic Example No.	Efficacy (%)	EC_{50} (ng/ml)
1	74	7.4
2	89	6.3
3	82	15
4	53	15
5	86	3.4
6	64	7.4
7	99	2.2
8	52	31
9	90	5.1
10	78	20
11	83	2.0
12	100	76
13	99	280
14	91	72
15	109	23
16	58	61
17	73	79
18	94	55
19	100	14
20	91	38
21	39	290
22	50	190
23	129	28
24	89	7.2
25	54	200
26	78	2.9
27	75	5.6
28	99	37
29	67	230
30	106	19
31	63	5.2
32	90	37
33	96	1.1

34	99	5.2
35	99	34
36	97	59
37	63	140
38	93	36
39	97	28
40	37	250
41	115	32
42	71	250
43	87	83
44	26	250
45	74	30
46	82	15
47	48	190
48	62	8.0
49	62	9.1
50	89	37
51	73	33
52	22	120
53	120	12
54	61	7.5
55	53	220
56	96	1.1
57	97	5.9
58	110	32
59	82	24
60	62	100
61	91	29
62	57	6.4
63	21	190
64	74	7.7
65	70	8.9
66	133	33
67	80	33
68	26	210
69	89	5.7

70	87	23
71	89	69
72	88	75
73	84	10
74	77	25
75	89	63
76	79	46
77	78	5.1
78	69	15
79	81	160
80	71	640
81	84	7.2
82	84	26
83	78	6.1
84	109	130
86	105	21
87	71	600
88	70	130
89	68	39
90	76	21
91	81	24
92	82	5.5
93	84	4.3
Reference Synthetic Example 1	7	-
Reference Synthetic Example 2	12	-
Reference Synthetic Example 3	7	-
Reference Synthetic Example 4	67	1400

ASSAY EXAMPLE 4

Synthetic Example 56, the compound of the present invention, and four compounds (Reference Synthetic Examples 1 to 4) described in a publication of international patent application, Publication No. WO01/34585, applied by SmithKline Beecham Corp. were tested according to the method of Assay Example 1. Figure 3 shows the results.

ASSAY EXAMPLE 5

Activity of Stimulating Proliferation of a Thrombopoietin (TPO)-dependent Cell Line (2)

Human leukemic cell line UT7/EPO-mpl was washed twice with PBS and suspended in IMDM containing 10% fetal bovine serum at a cell density of 6×10^4 cells/ml. The cell suspension was transferred to a 96-well tissue culture plate (CORNING) in 100-µl aliquots. Then the following Synthetic Examples, each dissolved in DMSO, were diluted 83-fold with IMDM containing 10% fetal bovine serum and added to the aforementioned cell suspension in 20-µl aliquots. The suspension was incubated in a CO_2 incubator (5% CO_2, 37°C) for 4 days. Cell proliferation was assayed using WST-8 reagent (Kishida Chemical, Co. Ltd.) according to instructions by the manufacturer. A 10-µl aliquot of 5 mM WST-8 reagent solution was added to each well of the tissue culture plate, and the plate was incubated at 37°C for 4 h. The formazan pigment generated was detected by measuring the

absorbance at 450 nm with a 96-well microplate reader (Nihon Molecular Devices, Spectramax 190). The concentration of each compound that yields a growth rate corresponding to 50% of the growth of human leukemic cell line UT7/EPO-mpl observed in the presence of 10 ng/ml TPO ($EC_{50}T$) and the maximal growth rate achieved by the same compound (Efficacy), expressed by taking the value with human leukemic cell line UT7/EPO-mpl in the presence of 10 ng/ml TPO as 100% standard, are summarized in Table 9.

Table 9

Synthetic Example No.	Efficacy (%)	$EC_{50}T$ (ng/ml)
94	95	3.3
95	71	52
96	93	3.3
97	94	25
98	96	31
99	110	3.9
100	107	59
101	100	18
102	97	69
103	90	4.8

FORMULATION EXAMPLE 1

A granule preparation containing the following ingredients is prepared.

Ingredients

Compound represented by the formula (1)	10 mg
Lactose	700 mg
Corn Starch	274 mg
HPC-L	16 mg
	1000 mg

A compound represented by the formula (1) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed in a V-type blender. The powder mixture is kneaded with a low-viscosity hydroxypropylcellulose (HPC-L) aqueous solution, granulated (extrusion granulation, die size 0.5-1 mm) and dried. The resulting dry granules are sifted through a shaking sieve (12/60 mesh) to obtain a granule preparation.

FORMULATION EXAMPLE 2

A powder preparation for capsulation containing the following ingredients is prepared.

Ingredients

Compound represented by the formula (1)	10 mg
Lactose	79 mg
Corn Starch	10 mg
Magnesium Stearate	1 mg
	100 mg

A compound represented by the formula (1) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed with magnesium stearate in a V-type blender. The 10% powder is put in hard capsules No. 5, 100 mg each.

FORMULATION EXAMPLE 3

A granule preparation for capsulation containing the following ingredients is prepared.

Ingredients

Compound represented by the formula (1)	15 mg
Lactose	90 mg
Corn Starch	42 mg
HPC-L	3 mg
	150 mg

A compound represented by the formula (1) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed in a V-type blender. The powder mixture is kneaded with a low-viscosity hydroxypropylcellulose (HPC-L) aqueous solution, granulated and dried. The resulting dry granules are sifted through a shaking sieve (12/60 mesh). The granules are put in hard capsules No. 4, 150 mg each.

FORMULATION EXAMPLE 4

A tablet preparation containing the following ingredients is prepared.

Ingredients

Compound represented by the formula (1)	10 mg
Lactose	90 mg
Microcrystalline cellulose	30 mg
Magnesium Stearate	5 mg
CMC-Na	15 mg
	150 mg

A compound represented by the formula (1), lactose, microcrystalline cellulose and CMC-Na (carboxymethylcellulose sodium salt) are sifted through a 60-mesh sieve and mixed. The powder mixture is mixed with magnesium stearate to give a bulk powder mixture. The powder mixture is compressed directly into 150 mg tablets.

FORMULATION EXAMPLE 5

An intravenous preparation is prepared as follows.

Compound represented by the formula (1)	100 mg
Saturated Fatty Acid Glyceride	1000 ml

Solutions having the above-mentioned composition are usually administered to a patient intravenously at a rate of 1 ml per 1 minute.

【Industrial applicability】

The compounds of the present invention which have affinity for thrombopoietin receptor and act as thrombopoietin receptor agonists are useful as preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective, especially as drugs for hematological disorders accompanied by abnormal platelet count and as drugs for diseases treated or prevented by stimulating differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells, and are useful as medicines.

【Brief description of drawings】

【Fig. 1】

The proliferation of UT7/EPO-mpl cells when stimulated by a compound of the present invention (Synthetic Example 56) assayed by the MTT method.

【Fig. 2】

The proliferation of UT7/EPO cells when stimulated by a compound of the present invention (Synthetic Example

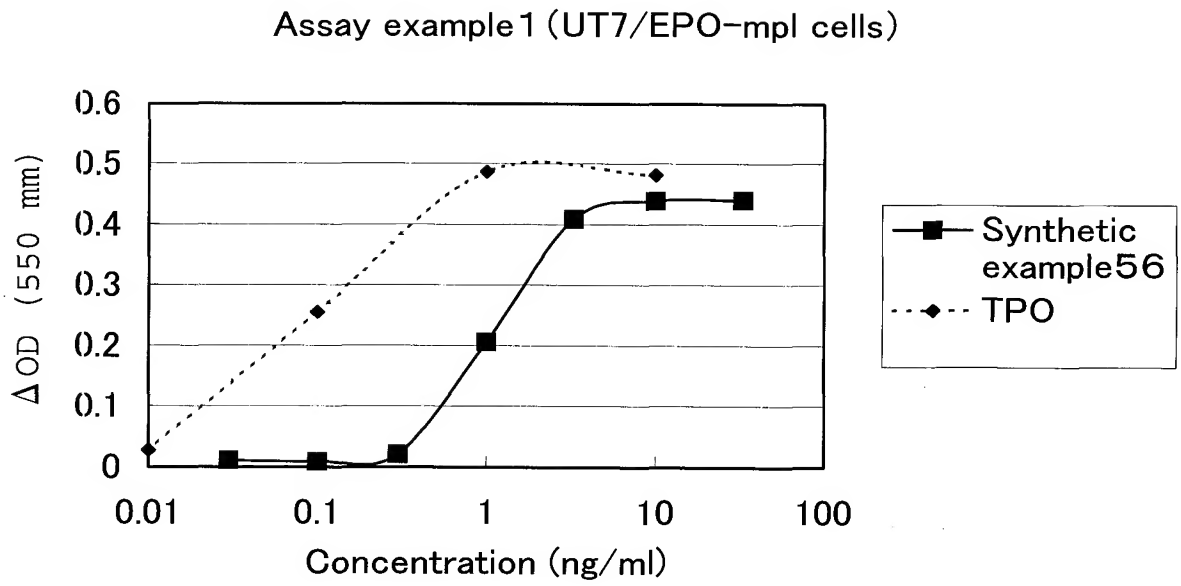
56) assayed by the MTT method.

【Fig. 3】

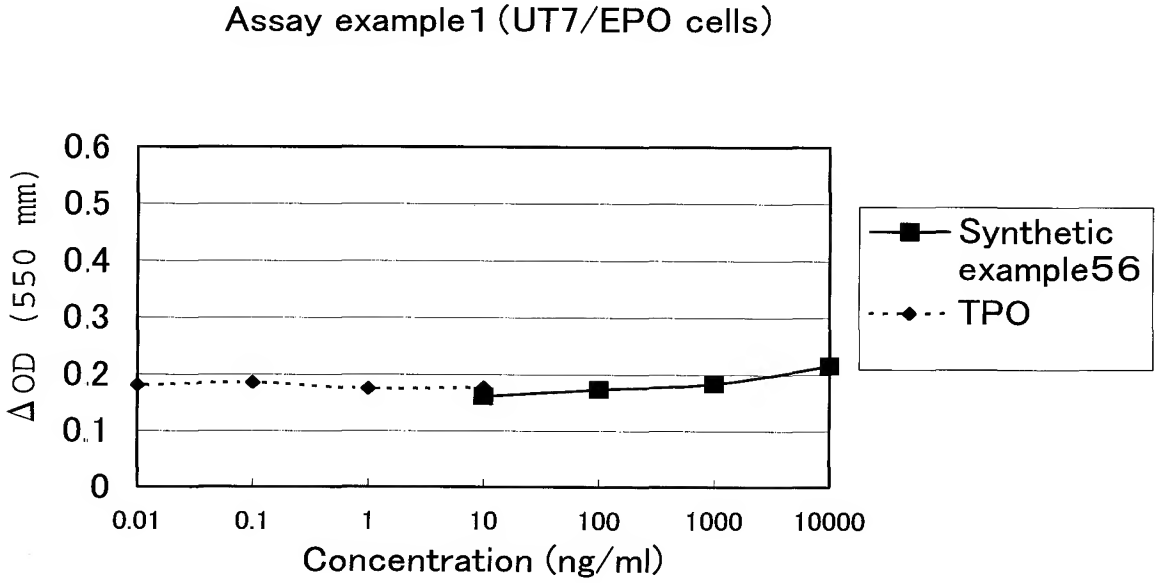
The proliferation of UT7/EPO-mpl cells when stimulated by a compound of the present invention (Synthetic Example 56) or the compounds described in a publication of international patent application (Reference Synthetic Examples 1 to 4) assayed by the MTT method.

【Type of Document】 DRAWING

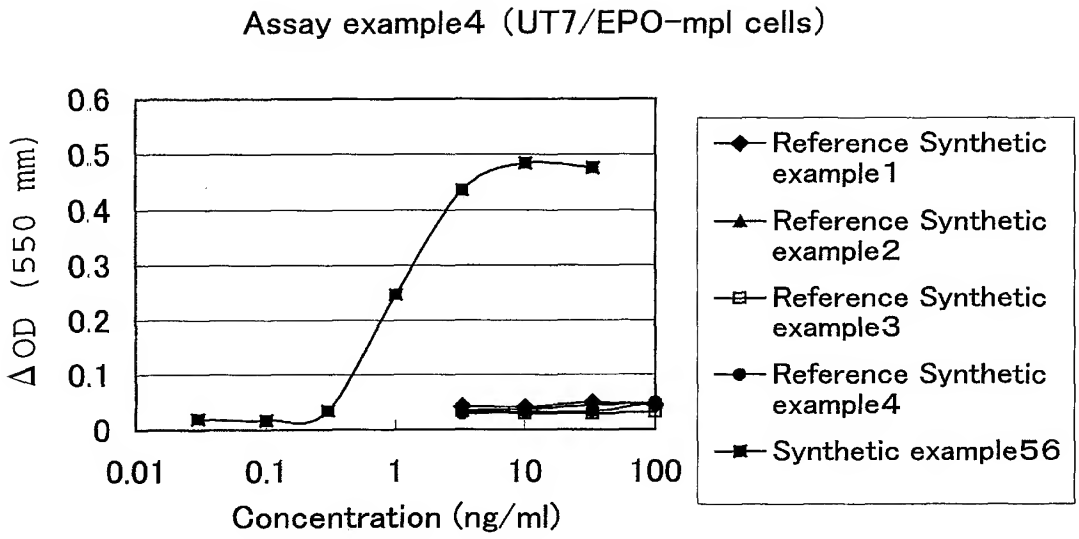
【Fig. 1】



【Fig. 2】



【Fig. 3】


Assay example4 (UT7/EPO-mpl cells)
ΔOD (550 mm)
0.6
0.5
0.4
0.3
0.2
0.1
0
0.01
0.1
1
10
100
Concentration (ng/ml)
Reference Synthetic example1
Reference Synthetic example2
Reference Synthetic example3
Reference Synthetic example4
Synthetic example56

【Type of Document】 ABSTRACT

【Summary】

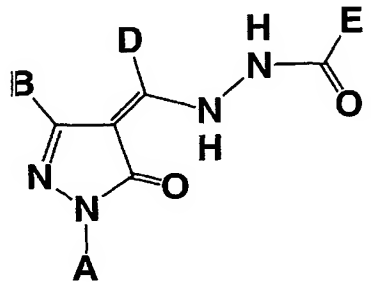
【Object】

To provide a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective.

【Means for solving problem】

A preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective or a platelet increasing agent, which contains a thrombopoietin receptor activator represented by the formula (1):

【Ka 1】



(1)

[wherein A is a C_{2-14} aryl group, B is hydrogen, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, D is hydrogen, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{2-14} aryl group, and E is a C_{2-14} aryl group], a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【Selected Figure】 No Selected Figure